Journal of Metals, Materials and Minerals, Vol. 33, No. 2, pp. 1-15, 2023

pH-responsive polymeric nanostructures for cancer theranostics

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Received date:
18 January 2023
Revised date
17 May 2023
Accepted date:
30 May 2023

Keywords:
pH-responsive polymer;
pH-triggered drug release;
Cancer theranostics;
pH-sensitive nanocarriers;
Modification strategy

Abstract

Responsive polymeric nanostructures are being designed to improve the efficiency of existing treatment techniques by delivering therapeutics in precise locations. The properties of the particles can be altered to act as a probe for imaging applications also. Hence, an effective theranostic agent can be tailor-made to meet the requirements. The pH variability has aroused considerable interest in nano-responsive-stimulus production since the mild acidic condition is a hallmark of the tumor microenvironment. The cargo sealed inside the carrier will be released either by swelling or disassembly of the carrier as they meet a pH drop. The modification strategy for the synthesis of pH-responsive polymers is discussed in the manuscript. Fabrication of pH-responsive theranostic agents can conquer major limitations of conventional treatment techniques. Herein we reported imperative insights on recent pH-sensitive polymeric nanomaterials for the treatment of various disease conditions, especially cancer.

1. Introduction

Despite the advancements in medical science, delivering a payload in a biological environment with desired therapeutic effects and the aftereffects of medications still remain a major challenge. The bio-distribution and clearance mechanisms are the two major factors that determine the efficacy of drugs, and therefore developing a sophisticated drug delivery system is of primary focus. The nano-technological approach is regarded as the best solution to modulate and overcome the issues faced by conventional drug delivery systems [1-3]. The efficiency of nanomaterials can be upgraded by transforming them into intelligent systems, *i.e.*, by designing materials that can respond to various internal and external stimuli like pH, temperature, redox, ROS, ultrasound, magnetic field, light, allowing delivery of drugs in a controlled and targeted location (Figure 1) [4]. Among various stimuli, inducing pH sensitivity in nanoparticles (NPs) has been regarded as one of the most effective platforms for the selective release of drugs since pH varies for every tissue, organ, and cell and also between normal and cancerous tissues. Combinational responsiveness is also being widely explored as it provides significant therapeutic effects. These combinatorial effects can be either one of two conditions, parallel or amplification. Parallel effects describe that the responsive behavior of one group never affects the other and is called an orthogonal response system, whereas in the second case, the behavior of one group is dependent on the other as it stimulates or amplifies the other group. These kinds of interplay between two sensitive groups greatly contribute to a successful drug delivery system [5-7]. Polymer nanoparticles are capable of protecting fragile cargo from leakage at undesired locations mostly due to their tunable size, surface modifications, and high surface area and biodistribution, thanks to the advancement of material science [8,9]. The nanoparticles can respond to various pH gradients by altering their surface chemistry, size, or architecture to release the payload. Nanocarriers are usually made into smart carriers by introducing an appropriate polymer to them. The polymeric nanostructures are capable of prolonging the drug's half-life in the bloodstream compared to other structures [10-12]. Polymers with ionizable residues get ionized in response to the pH of the solution. Incorporating polymers onto nanoparticles is achieved by various interactions, such as electrostatic interactions, hydrophobic interactions, and host-guest interactions. The strength between the bonding of NPs and polymers greatly contributes to the composite characteristics and also accounts for the final therapeutic effect [13]. This bonding strength can be improved by functionalizing the surface

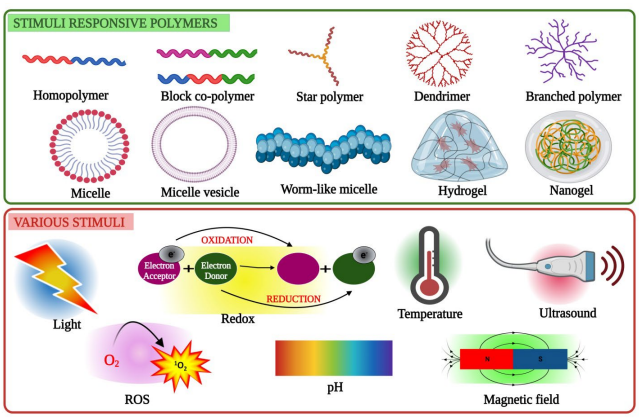

Figure 1. Various internal-external stimuli and their sensitive polymers

of the particle with various surface active groups, which are selected based on the application planned [14-17]. Introducing the drug-loaded polymers into a different pH condition will lead to a loss of structural integrity, leading to the release of cargo. Among the natural and synthetic polymers, naturally produced polymers are always preferred due to their availability, biocompatibility, and ease of modification. The modification strategy, mechanism of action, and its applications are discussed in the later part of the manuscript.

2. Role of pH in the tumor microenvironment

Cancer emerged as a persistent burden to both developing and developed nations [18]. Prolonged exposure to carcinogens eventually leads to the formation of cancer with high progression and metastasis of the disease [16]. Though this may not only be the precise cause of progression, the tumor microenvironment also plays a major role in it [16,19]. The researchers are fascinated by the role it has in the progression and control of tumor cells [20,21]. These lead the way to developing new drugs and interventions to control and treat tumors [22]. Cancer or cancer stem cells are sited in these environments, which encircle the endothelial cells, macrophages, cell signaling molecules, fibroblasts, blood vessels, ECM, T-lymphocytes, immune cells, lymphatic vessels, etc. [23]. For a tumor to grow and metastasize, they require an expanded blood supply deriving from normal blood vessels and promoting angiogenesis. Tumor blood vessels often fail to mature and are characterized by structures that are leaky, tortuous, and irregular in shape. These ultrastructural modifications lead to the leakage of tissue fluids into the microenvironment and increase the pressure of the fluid present in the interstitial region. The angiogenic tumor vessels and normal vasculature are distinguished by a large number of endothelial cell surface receptors, proteins, and ligands [24]. The intracellular cytoplasmic pH of normal differentiated cells is approximately 7.2, and the extracellular pH of the same is maintained at 7.4, whereas the cancer cells have hyper-acidic extracellular pH in the range of 6.5 to 6.9. The acidic nature of the tumor environment provides the essential nutrients and oxygen for the proliferation and invasion of the tumor when compared to normal cells [25]. There are two major parts that make the microenvironment acidic, *i.e.*, lactic acid and carbon dioxide [16]. For the past decades, lactic acid has been known as a waste product of cancer metabolism which gets generated through reprogrammed energy metabolism. Still, researchers have found that lactic acid has subsequent effects on cancer biology and is used in angiogenesis stimulation, etc. [26]. The extracellular and intracellular pH of both normal and tumor environment differs. Due to this, an ideal drug delivery system has emerged to be significant in improving the sensitivity and efficacy of chemotherapeutic drugs with less toxicity [20]. The cancerous cells were made resistant to numerous anticancer drugs because of the acidic extracellular pH, which gives rise to secondary tumor growth. By modifying the tumor environment either as a non-acidic environment or as a pH-responsive, nanoparticles release the payload when it reaches the acidic environment [27]. Due to the numerous functional capacity like biocompatibility, less toxicity, and biodegradability of polymeric nanoparticles, the researchers were attracted and designed various polymeric nanoparticles in various biomedical, agricultural, and industrial applications. These nanoparticles were known as multi-functional polymeric nanoparticles [28]. To increase these functional capacities, the polymer surface can be modified by integrating amide, ester, urea, or carbonate in their backbone. When a polymer encounters structural and conformational changes, it responds according to differential environmental conditions like temperature, light, pH, electrical field, salt, magnetic field, or ionic strength. Only natural or synthetic polymers or adding a responsive substance or function along the backbone of an already existing polymer may be used to create stimuli-responsive polymers. Biological, chemical, and physical are the three different types of environmental stimuli. The pH-responsive polymers behave according to their surrounding environment by going through some structural and functional changes. In reaction to changes in the surrounding pH, pH-sensitive polymers include acidic or basic groups that may either absorb or donate protons. The ionizable pH-responsive polymeric nanoparticle are used as a drug delivery system with various formulations like ionic interaction, surface modification, encapsulation the polymer onto the drug, core-shell nanoparticle for cancer therapy [29-31].

3. Modification strategies

There are three main strategies involved in designing the pH-responsive nanoparticles, 1) Charge-shifting polymers, 2) Polymers with H^+ labile linkages 3) Crosslinked particles (Figure 2).

3.1 pH-responsive charge-shifting polymeric nanoparticle

The pH-responsive materials are designed using a simple and effective approach using building blocks of polymer. The charge and hydrophilic properties of polymer-based building blocks change based on their pH. The change in the properties may be used to bring alterations such as rearranging, swelling, and disassembling in nanoparticle structures. Charge shifting happens in accordance with the pKa of the polymer [32]. The cationic polymers change from hydrophobic to positive charge/hydrophilic, and anionic polymer undergoes a change from negative charge/ hydrophilic to hydrophobic as the pH drops in the two cases.

3.1.1 Charge shifting depending on pH decreased from hydrophobic to hydrophilic

The polymers will shift to hydrophilic from hydrophobic when the pH falls below the pKa. These polymers will have an amino group

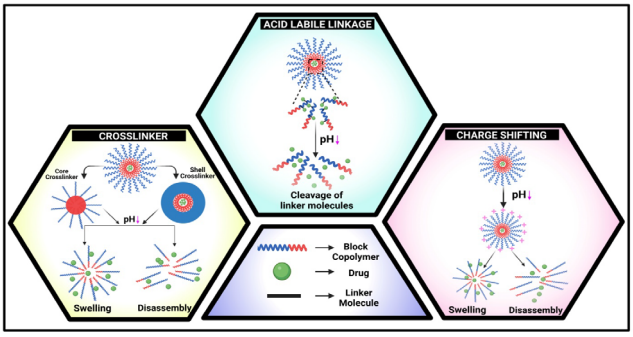

Figure 2. Modification strategies for pH-responsive polymers

such as poly (histidine), [poly(2-(diisopropylamino) ethyl methacrylate), and poly (4-vinyl pyridine). When the pH drops below their pKa, the amino group will accept the proton and become hydrophilic.

Liang *et al.* used an approach to synthesize one step delivery system by using nanoparticles which include a model drug like poly (ethylene glycol)-doxorubicin (dox) conjugate and PDPAEMA homopolymer [33]. They conjugated H4R4 peptide that consists of histidine and arginine groups. The PDPAEMA underwent a transition from a hydrophobic to hydrophilic nature, which caused disassembling of nanoparticles and released dox conjugate in an acidic condition. The release of the drug was pH dependent, which was demonstrated by the release of dox. They released only 10% at pH 7.4 and 90% release after 36 h at pH 5.5. When there is a loading of nanoparticles with the H4R4 peptide, it causes a 30-fold increase in cytotoxic effects. The *in vitro* experiments using HeLa cells showed the incorporation of H4R4 promotes the restriction of dox into the nucleus. The mean size of the nanoparticle is 150 nm. By using calcein, the endosomal escape caused by the nanoparticles was investigated and showed greater drug release and escape of nanoparticles [33]. Wilson and co-workers used the charge-shifting polymer to design a vaccine delivery system. His group designed and synthesized a pH-responsive nanoparticle of 23 nm. DEAEMA in the hydrophobic block was used for the complexation of oligonucleotide adjuvant (CpG ODN). Through disulfide exchange, PDSEMA was used for the incorporation of ovalbumin (OVA) as a thiolated protein antigen. The butyl methacrylate (BMA), DMAEMA, and propyl acrylic acid are based on the pH-responsive hydrophobic blocks. When the nanoparticle is exposed to low pH, they involve disassembling, interacting with the endosomal membrane, and releasing their antigen. In this study, they reported that compared to free OVA-vaccinated mice, the OVA-conjugated vaccination mice showed higher CD8· T cell response [34]. Zhou and their team planned a well-designed block copolymer system by using a hydrophilic component, which includes poly(ethylene oxide) and hydrophobic blocks with a series of tertiary amine monomer (PR block) to make a pH–activated micellar system. In the initial work, the pH dissociation of the micelles can be changed by using a different combination of ionizable hydrophobic blocks. The functionalized PR blocks were prepared by two types: 1) a sequence of linear dialkyl moieties which consist of different chain lengths from the methyl to butyl groups, and 2) a cyclic sequence in which the circle size is changed from 5- to 7- membered rings. To investigate the pH-dependent response, the authors conjugated the pH-insensitive dye tetramethyl rhodamine in respective micelles. When the pH is higher than the pKa of the responsive micelle system, the PR group is hydrophobic, which results in the self-assembling of the particles and the extinction of fluorescence signals through photoinduced electron transfer and homo-FRET. The PR group becomes protonated when the pH is lower than pKa, which causes disassembling of micelles and an increase in fluorescence. Using this technique, they could regulate the internalization of particles into endosomal or lysosomal cell partitions by following an increase in fluorescence intensity. At low pH, the complex of PDMAEMA-b-PDPAEMA or siRNA dissociated, and the release of hydrophobic amphotericin B is achieved [35].

3.1.2 Charge shifting depending on pH decreased from hydrophilic to hydrophobic

By using polymer synthesize from the acidic monomer such as poly(aspartic acid) [36], poly (methacrylic acid) [37], and sulfonamide-based polymers [38], it is possible to engineer a nanoparticle delivery system responsive to a decrease in pH in which it becomes more hydrophobic [39]. Kang *et al.* developed sulphonamide-based oligomers (OSA), which were negatively charged, that shift from hydrophilic to hydrophobic with a drop in pH with proton buffering capacity. They turned the pKa of OSA from 3 to 11 based on the choice of the side chain, such as sulfadimethoxine, sulfamerazine, sulfamethizole, etc. In the transition of OSAs, they investigated proton buffering and pH-based solubility. In the pH range between 5 to 6.4 and 5.7 to 7.3, the oligosulfamethizole (OSMT) and oligosulfadiazine (OSDZ) had broad proton buffering. The proton buffering of OSMZ and OSDM occurs only at 6.5 and 7.3 pH. To investigate the *in vitro* delivery of nucleic acid, they used different cell lines. By joining the sulfonamide polymer with the DNA and then complexing with the poly(L-lysine), OSA-polyplexes were designed. Against the cell HEK293 and RINm5F, the OSMZ and OSDZ polyplexes have maximum transfection compared to PLL/DNA. When the pH decreases, the functional group becomes hydrophobic and enhances the destabilization of the endosomal membrane, and facilitates the endosomal escape [40]. Wang and team fabricated a PLGA-b-poly (D, L-lactic acid) based micelles loaded with dox for the treatment of melanoma. Under the acidic condition of the tumor, the PLGA blocks underwent conformational changes that triggered the dox to release. The dox exhibited increased release under acidic conditions. A *in vivo* model of tumor-bearing mice was utilized to study the efficiency of the prepared particle. The study model was evaluated with NIR imaging technology. The experimental results showed that the hybrid material developed showed high drug release in acidic conditions [41].

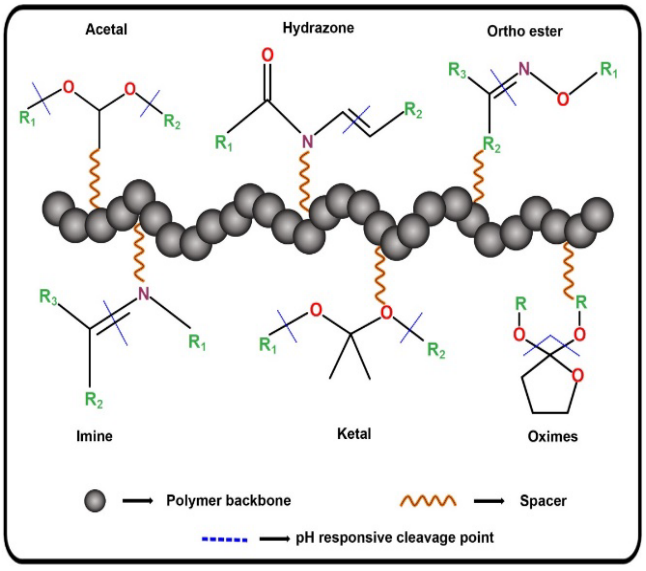

Figure 3. pH-responsive cleavage of acid-labile linkages

3.2 pH-responsive polymers with acid-labile linkages

Acid-cleavable bonds play an important role in pH-responsive nanoparticles by acting as the linker of PEG and the backbone of polymers [42]. The pH-sensitive chemical linkages polymers, such as ortho ester, acetal, hydrazone, imine, and pH-sensitive cell-penetrating peptides respond to acidic compartments of endosomes or lysosomes to release any cargo by undergoing pH-dependent protonation (Figure 3) [43].

3.2.1 Acetal/ketal linkages

Acetals and ketals are normally exceptional in pharmaceuticals, yet, they are present in some prodrugs [44]. Acetal linkages are used for constructing drug/gene delivery carriers. Acetals help in the linkages of alcohol functionalities. It is the potential to adjust its hydrolysis rate by changing its chemical structure [45]. The acetals used in drug delivery as pH-sensitive linkages were first described by Gillies *et al.* [46]. The significant work here was using acetal linkages for the formation of the hydrophobic nanoparticle. The degradation in the linkages occurs when the properties of the particle change from hydrophobic to hydrophilic as the pH drops, thus making it easier for drug release [47]. Suarez *et al.* changed the ratio of cyclic acetals to acyclic by varying the dextran acetalation reaction time. This strategy was used for postmyocardial infarction (MI) treatment for which the requirement of drug release is over several weeks, which is done by the Ac-Dex (acetalated dextran) degradation rate [48]. There were many modifications in Ac-Dex, which have also been reported by many authors. It was reported that micellar nanoparticles were combined with PEG- b- PAA copolymers by Gu and co-workers. PAA was tagged with vinyl ethers and loaded with paclitaxel drug (PTX) [49]. It was demonstrated that up to 43 wt% of PTX can be loaded into the particles. By physical encapsulation, dual drugs (PTX and dox) can be encapsulated into the nanoparticles to perform pH-triggered release [50]. These acetal-based pH-responsive drug delivery system developments may guide scientists in treating various diseases [51]. One such example is the effect of modifications in the architecture upon the pH-sensitive polymer-based nanogels construct [52].

3.2.2 Ortho ester linkages

The ortho ester linkages are regarded as a functional kind of biodegradable linkage that is capable of responding to the pH environment. It was Huang and their team who built-in polymers with ortho ester linkages as a pendant group [50]. Microspheres made of poly(orthoester) (POE) have previously been shown to have certain advantages in the *in vivo* delivery of DNA vaccines. Specifically, the timing of DNA discharge from POE microspheres in acidic phagosomal pH was demonstrated to be the significant factor in deciding immunogenicity, which was theorized to be connected to the characteristic movement of antigen-introducing cell take-up, transfection, and antigen introduction [53]. Li & co-workers described that, in a physiological environment, the acid-degradable nanogels and non-sensitive nanogels have tremendous stability and consistent size. The ortho ester crosslinking agent crossed-linked with CMCS (carboxymethyl chitosan) to produce acid-degradable nanogels and crossed-linked with EDGE (ethyleneglycol diglycidyl ether) to produce non-sensitive nanogels [54]. Tang and others have reported on PEG-b-polymethacrylamides containing acid-labile ortho ester side-chains and characterized in detail the pH-sensitive side-chain hydrolysis and its influence on the physicochemical properties of the block copolymer micelles. Although it has been proposed that such amphiphilic block copolymers with acid-labile side-chains may be promising nanocarriers for hydrophobic anticancer drugs, the incorporation and release of actual drugs from such block copolymer micelles and the efficacy of killing cancer cells have not been demonstrated [55]. The recent studies based on the modification strategies are given in the Table 1.

Table 1. Summary of polymer linkages applied in the theranostic applications.

S. No	Linkages/modifiers	Conjugation	Polymer	Drug	Application	Disease condition	Ref.
1.	Hydrazone bond	Covalent conjugation	Bi(poly(ethylene glycol)–poly(lactic acid)) (PEG-PLA)-platinum(IV)	Cisplatin	Drug delivery	Ovarian cancer	[56]
2.	Hydrogen bond	-	Uracil conjugated poly(p-phenylene vinylene)	Dox	Drug delivery	Cervical cancer	[57]
3.	Imine bond	-	Pentaerythritol tetra(3-mercaptopropionate)-allylurea-PEG	Dox	Drug delivery	Osteoblastic metastases	[58]
4.	Benzoic-imine bond	-	PEG-Chitosan	Indocyanine green	Cancer theranostics	-	[59]
5.	Acetal bond	-	Aliphatic polycarbonates	Paclitaxel	Drug delivery	Lung cancer	[60]
6.	Crosslinking with Calcium ions	-	Poly(N-Isopropylacrylamide-co-Vinylsulfonic acid)/Alginate	Dox	Drug delivery and wound healing	-	[61]
7.	Amide bonds	-	Carbon polymer dot nanoparticles	-	Imaging	Cancerous cells	[62]
8.	Ortho ester bonds	-	PEG	Dox	Drug delivery	Breast cancer	[63]
9.	Oximes bond	-	Amphiphilic block copolymers - Poly(2-(diisopropyl)aminoethyl methacrylate (DPA)	Nile Red and rhodamine 6G dyes (for delivery potential evaluation)	Drug delivery	Lung and breast cancer	[64]
10.	Hydrazone bond	-	PEG/Hydroxypropyl methacrylamide based polymer	Dox	Drug delivery	Breast cancer	[65]

3.3 Crosslinking in pH-responsive nanoparticles

Maintaining particle stability is the main challenge in nanoparticle delivery systems because self-assembled materials can change the structure. Stabilizers and crosslinking can improve the stability of nanoparticles [66]. Crosslinking is done by the covalent interactions and non-covalent interactions [67]. Though the release of a drug to a target is limited, irreversible crosslinking is a disadvantage for some applications. When the targeted site is reached the reversible crosslinking breakdown, some examples of degradable crosslinkers are pH-sensitive disulfide derivatives [68]. This shell-crosslinked structure improved the storage stability of the NPs and prevented some drug leakage. These nano-carriers based on covalent connections might keep cargo stable for a long time, but the production of crosslinked structures based on noncovalent bonds requires a chemical reaction, which adds to the experiment's complexity [69]. The core-shell nanogels using free radical polymerization of poly(Nisopropylacralamide) (PNIPAM) under the presence of N-lysinal-N-succinyl chitosan (NLSC) with N, N-methlene bisacralamide (MBA) were synthesized as a crosslinker by Han *et al.* Using bovine serum albumin (BSA) the core were personalized, and a capsid was crosslinked like a shell on the core. By replacing the (NLSC) N-lysinal-Nsuccinylchitosan with NLC (N-lysinal chitosan), a non-swellable particle was developed. From 200 nm at pH 7.4 to 2 μm at pH 4, a large swelling was detected by N-lysinal-N-succinyl chitosan (NLSC). There is no swelling seen in the non-responsive nanoparticle. It is confirmed that the dox-NLSC produces red fluorescence, and the control particle produces fluorescence on the edge of the outer layer [70]. The aldehyde group can react with the amine group by the cross-linkage of glutaraldehyde. The Schiff Base was fashioned by the nucleophilic attack of the amino group (nitrogen), which is present in the carbon of glutaraldehyde [71]. In the drug delivery system, there is some important responsibility with glutaraldehyde, that is, innate toxicity [72]. Poly(lysine)-b-poly(caprolactone) (PLL-b-PCl) was used as a nanoparticle core by Tang & co-workers. It was crosslinked with glutaraldehyde. To form the poly ion complex micelle, poly (glutamic acid)-g-methoxyl and poly(ethylene glycol) (PGlu-g-mPEG) were added. When the pH decreased, the PGlu-g-mPEG coating was released because they were pH dependent. Based on the percentage of the cross-linkage, the charge reversal rate can be adjusted. It is revealed that the delayed charge reversal has side effects on increasing tumor penetration [73]. Studies have shown that the stability of the nanoparticles is improved before they reach their target site, which is one of the advantages of cross-linking. Nanoparticle cleavage can be slow, which depends on the degradation of covalent bonds when the difference between the physiological pH and cleavage environment is small. Therefore, non-covalent strategies are of interest, such as the polyphenol and the complexation of iron. The specificity of the drug release is improved by the combination of different crosslinking moieties and has a stimulating direction for future research [74].

4. pH and associated dual responsiveness

Taking advantage of the special ambiance of the tumor microenvironment, particles capable of responding to multiple stimuli can be designed to obtain superior therapeutic potential. As already discussed, the synergistic effect obtained from the combination of functional groups that are sensitive to different stimuli will yield a much better therapeutic effect when compared with a single moiety. These statements can be proved with scientific evidence, which is discussed in the latter section. The pH-responsive behavior of the nanopolymers, combined with other stimuli, is widely being studied. Among the other stimuli, the combinatorial effect of pH with stimuli like temperature, redox, and ROS is being widely explored. The manuscript focuses on these three combinations, while the other combinations are tabulated in Table 2.

4.1 pH/ redox responsiveness

The combination of pH and redox responsiveness of a single polymer entity will help to acquire many benefits since the number of reducing species in the tumor microenvironment is comparatively more [75,76]. The tumor microenvironment possesses numerous different characteristics compared to healthy cells. As the concentration of the reducing species, GSH (Glutathione) in tumor cells is more, linkages that could respond to GSH, such as disulfide or diselenide, can be incorporated on the surface of the particle to develop a redox-responsive drug delivery system. When these linkages are added to a polymer like chitosan, which has the inherent pH-responsive property, the drug delivery of chemotherapeutics can be achieved more selectively due to dual responsiveness [77]. Wang *et al.* recently fabricated dual responsive polymeric micelles to perform dual drug delivery of dox and paclitaxel. The group used dimethylmaleic anhydride (DMMA) to induce pH sensitivity to the micelle and disulfide bonds for reduction responsiveness. The particle surface was modified with folic acid as a targeting moiety. It was noticed that the particle exhibited charged shift from negative to positive when introduced into physiological pH. This behavior of the particle helps with cellular internalization toward the tumor microenvironment. The *in vivo* study with a lung cancer-induced mice model displayed improved tumor inhibition efficiency with dual drug delivery [78]. To acquire dual therapy of magnetothermal and chemotherapy, Zhao *et al.* used magnetic mesoporous silica nanoparticles to perform pH and redox-sensitive therapy. The fabrication consists of core-shell nanoparticles with iron oxide as the core, mesoporous silica nanoparticles as the shell, and surface modification with chitosan and folic acid. The *in vitro* study results showed improved selectivity, high cytotoxicity, and strong tumor inhibition. These multifunctional nanoplatforms featured high bioavailability, good biocompatibility, and high biosafety [79]. Similarly, Falsafi *et al.* developed nanosized polymer particles with dual (pH/redox) responsiveness, but this time for theranostic application. The vehicle was prepared with dithiodiglycolic acid and iron chloride, coated with an amphiphilic copolymer, and decorated with an aptamer to deliver dox. The iron chloride in the vehicle helped in MR imaging, thus providing image-guided therapy. The *in vivo* study experiments showed great drug internalization and high cytotoxicity provided with monitoring through MR imaging system towards breast cancer in breast cancer-induced mice model [80].

4.2 pH/ ROS responsiveness

The incorporation of reactive oxygen species (ROS) responsive block would provide photodynamic therapy (PDT) when introduced to light. As the excitation of oxygen with light leads to the production of ROS which is capable of killing cells, bonds that undergo cleavage in response to such conditions can deliver the drug at appropriate sites, thereby reducing the adverse effects. ROS being an endogenous stimulus, are present in higher concentrations at the tumor site. Thus combining pH and ROS sensitivity to the particle can yield dual therapy of chemotherapy and PDT. A research group of Ding recently developed a supramolecular polypeptide prodrug capable of possessing pH/ROS response. For chemotherapy, dox was loaded onto the carrier. The particle exhibited charge-shift behavior when it entered the physiological pH. This charge reversal characteristic accounts for stability and site-specific delivery of the payloads. As a photosensitizer, chlorin e6 was used, which was irradiated at 660 nm to cleave the TK linker for the release of the drug [81]. Li *et al*. designed a nano-formulation of micelle encapsulated with pH-sensitive polymer and ROS-generating agent (β-lapachone) loaded with the drug paclitaxel. The particle, when it entered the tumor site, imparted pH-triggered drug release due to the transformation of the hydrophobic core to hydrophilic in the presence of an acidic environment and subsequently generated ROS providing a platform for photodynamic therapy synergistically confirmed *in vitro* and *in vivo* [82].

4.3 pH/ thermal responsiveness

The Lower critical solution temperature (LCST) is one of the major properties of polymeric substances in terms of temperature responsiveness, and so, to acquire temperature responsiveness, polymers with LCST are utilized. PNIPAM is considered one of the classic materials that are typically used to introduce temperature responsiveness onto a nanocarrier. PNIPAM, when it enters an environment with a temperature lower than LCST, undergoes a phase transition mechanism from hydrophobic to hydrophilic due to the formation of hydrogen bonds. These bonds between water molecules and amide groups are the primary reason for the transition. When PNIPAM enters an environment with a temperature higher than LCST, it disassembles due to the disruption of hydrogen bonds to release the payload. Owning to this, Liu *et al.* fabricated aerogel with carboxymethyl cellulose. PNIPAM was used to make the compound thermal responsive. The experimental results of the drug release of 5-fluorouracil showed a high response toward pH and temperature, which was analyzed through the drug release kinetics and swelling test. It was concluded that the aerogel prepared was nontoxic, and the reason behind the sustained drug release was Fickian diffusion [83]. Mdlovu *et al.* synthesized a nanodrug carrier with magnetic iron oxide nanoparticles. The particles were surface modified with two different polymers (pluronic f127 and polyethylenimine) and loaded with the dox drug. The *in vitro* study with liver cancer cells showed a high response to pH and temperature changes. The authors studied the release profiling and stated that the drug release followed Weibull model at temperature changes and power law, *i.e.*, the Korsmeyer–Peppas kinetics model at pH changes. The uptake of the drug by cells was studied with the fluorescence technique, which showed high fluorescence of dox when the magnetic field is altered. And so, the developed carrier possessed therapeutic potential [84]. Besides temperature, reducing environment, and ROS responsiveness, the pH-sensitive materials can be combined with the magnetic field, ultrasound, and light-sensitive materials for improved drug delivery, therapy, and imaging applications (Table 2).

Table 2. Compilation of pH and associated stimuli-responsive particles for biomedical applications.

Sl. No.	Carrier	Dual/multi stimuli-responsive system	Stimuli sensitive polymer	Drug used	Application type	Cancer type	Outcome	Ref.
1.	Fe_3O_4- Glycidyl methacrylate-Dextran	pH/ Temperature	pH - N-vinylimidazole monomers Temperature- N-vinylcaprolactam monomers	5-fluorouracil	Drug delivery system (DDS)	Breast cancer	A dual pH/temperature-responsive polymeric nano-carrier for a drug delivery system was synthesized for breast cancer. The designed drug delivery system has the advantage of loading a large amount of drug and maintaining it at alkaline pH, and released at acidic pH.	[85]
2.	Tremella polysaccharide and glycoside surfactant- decyl polyglucoside based hydrogel	pH/ Temperature	PNIPAM	Indomethacin	DDS	-	The synthesized WSK/ C10APG micelle-laden hydrogels act as a potential drug delivery vehicle and have great applications in many fields, including tissue engineering.	[86]
3.	Bentonite nanoclay-based nanocomposites	pH/ Temperature	Temperature- Poly(N-isopropylacrylamide) (PNIPA) pH- N-isopropylacrylamide (NIPA) and N, N′-methylenebis acrylamide	Erlotinib (ERL)	DDS	Lung cancer	These act as drug carriers for the treatment against lung cancer, which highly inhibits tumor cell growth and induces cell death. The formulation is found to be effective when administered orally	[87]

Table 2. (continued).

Sl. No.	Carrier	Dual/multi stimuli-responsive system	Stimuli sensitive polymer	Drug used	Application type	Cancer type	Outcome	Ref.
4.	A lanthanide doped upconversion nanoparticle (UNCP) core and a transformable poly-o-nitrobenzyl shell Core-shell based nanocomposite	pH/Light	pH- Hydrogen bonds and charge interaction between nanocapsule and dox Light- poly-o-nitrobenzyl shell	Dox	Therapy	-	The interaction of charge with Dox and hydrogen bonds triggers the drug release at low pH. High controlled drug release of drug was observed in the acidic medium with high NIR effect, which is used as a potential therapeutic agent for treating diseases.	[88]
5.	Fe_3O_4@SiO_2 magnetic nanoparticles	pH/ Temperature	pH- Hydrazine units Temperature- N - isopropylacrylamide (NIPAM)	Dox	Therapy	Cervical cancer	The synthesized magnetic nanoparticles grafted with polymer chains are a useful study material for tumor treatment. These materials exhibit dual stimuli responses and significant carrier for delivering dox at the tumor site.	[89]
6.	Six star block copolymeric micelle-based nanogel	pH/ redox/ UV radiation	pH- PAA Redox-GSH	Dox	DDS	Liver cancer	The multi-stimuli sensitive nanogels are highly degradable and biocompatible, which act as potential drug carriers for delivering the drug and releasing it under UV irradiation and rapidly suppressing the proliferation of tumor cells.	[90]
7.	The PEG-PMT copolymeric micelle	pH/ ROS	PEG-PMT	Docetaxel	DDS	Murine colorectal carcinoma	The drug-loaded PEG-PMT micelles carry out better functions than the readily available product Duopafei and have less toxicity on normal organs. These micelles are used as a carrier for delivering antitumor drugs and controlling their release at tumor sites.	[91]
8.	(γ-PGA-S-S-CS NPs) nanocarriers	pH/ redox	pH- poly-γ-glutamic acid Redox-glutathione	Dox	DDS	Cervical cancer	The drug-loaded nano-carriers were stable under the physiological condition with less toxicity on normal cells and released the drug in response to redox and pH. Hence these nanocarriers can be used as targeted drug delivery for cancer.	[92]
9.	Fe_3O_4@SiO_2 magnetic nanoparticles	Ultrasound/ redox/ pH	pH/redox- Lipoic acid (LA)-conjugated chitosan (CS) polymer	Dox	DDS	Breast cell	The synthesized triple-responsive hybrid nano-carrier easily released the drug at the tumor site and produced cell death in MCF-7 cells. Though it acts as a prospective controlled drug delivery system, it can be carried out for in vivo studies.	[93]
10.	Dual stimuli nanocarrier	pH/ ROS	pH/redox- ACD and OCD	Rapamycin	Therapy	-	The dual stimuli nanocarrier was highly assembled in the injured carotid arteries and exhibited better results both in an *in-vitro* and *in-vivo* study which can be used as nanovehicle for further restenosis therapy and other vascular inflammatory diseases.	[94]

5. Applications of pH-responsive polymers

Owing to its versatile properties, the pH-sensitive polymers can be used in therapy, imaging, and theranostic applications of tumors and other deadly disease conditions (Figure 4). Wu *et al*. reviewed the size variable pH-responsive polymeric nanocarriers for therapeutic and imaging applications. They described five strategies for designing size-variable pH-sensitive particles. 1) The size of the nanocarriers plays a vital role in performing a targeted release of payload since the small particles can easily escape the mononuclear phagocyte system, thereby minimizing the undesirable clearance rate and also possessing EPR (enhanced permeation and retention) effect; 2) To promote high uptake of pH-sensitive nanocarriers for high permeable tumors, the less acidic environment will be enough to perform aggregation of nanocarriers, which occurs through time and concentration-dependent interactions, 3) In order to penetrate poor permeable tumor condition, nanocarriers with size shrinking capability are highly favorable, 4) The pH-sensitive carrier once reaches tumor site, either swell or disassemble to release the payload, 5) The pH-sensitive nanocarriers can also be designed to act as a probe in imaging applications [95].

5.1 Drug delivery

Delivery of drugs with the least intensity of adverse effects is accomplished by targeted drug delivery. Nanoparticles are the kind of it and produce a specific site for the delivery of drugs. The fast improvised area of nanoparticles paved various approaches to drug delivery. For this reason, the efficiency of the drugs has been improved, and the side effects have been reduced [96]**.** Polymeric nanoparticles are one among them. Due to the large surface area, polymeric nanoparticles are a vastly searched area amongst researchers. It is used in many applications like drug delivery, cancer, implants, imaging, therapeutics, etc. [97]**.**

Palanikumar *et al.* synthesized pH-responsive hybrid nanoparticles, which are recyclable and biologically compatible. The communications of serum protein, as well as the macrophages, was reduced when the cross-coupled bovine serum albumin enfolded covalently on mitochondria targeting dox-TPP loaded polylactic co-glycolic acid core. The ATRAM-BSA-PLGA nanoparticles loaded with dox-TPP have highly potent pH-based cellular intake and have cytotoxicity in various cell line ranges of cancer. They emphasized the BSA-PLGA hybrid nanoparticle, which is ATRAM conjugated, provides great strength for targeted drug delivery of cancer [98]**.**

Sadhukhan *et al.* used the biologically active molecule quercetin conjugated with phenylboronic acid and zinc oxide nanoparticles for the treatment of breast cancer with progressive targeted therapy in Ehrlich cells [99]. Both *in vitro* and *in vivo* conditions performed programmed cell death in breast cancer, and also the tumor effect is lessened. When the sialic acid interacts, PBA-ZO-Q is liberated. The toxicity of tumors in the spleen, kidney, and liver was also lessened. They concluded that, by increasing the quercetin effect, the anticancer activity could be improved, and the pH-responsive activities are seen in the quercetin-loaded PBA-ZNO nanoparticle and can be used in clinical treatment [100, 101]**.**

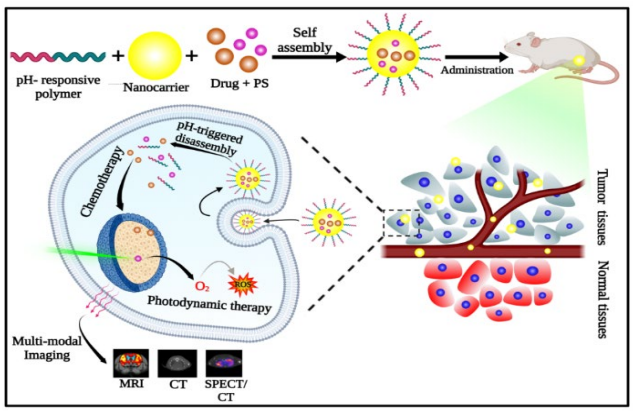

Figure 4. Application of pH-responsive polymer nanoparticles

In a similar way, Kundu *et al.* synthesized a phenylboronic acid conjugated pH-sensitive zinc oxide nanoparticle loaded with the biologically active molecule curcumin, which acts as a delivery system and provides a targeted therapy in breast cancer treatment. In *in vivo* study, the PBA-ZO-Curcumin, when interacting with sialic acid present in the cancer cell, reduced the tumor condition and showed decreased toxicity level in the Ehrlich cell. Intravenous administration is found to be the most effective route of administration. They concluded that the ZNO-PBA-Curcumin provides a potential chemotherapeutic treatment for breast cancer and also showed a pH-sensitive action and was used in future clinical trials [102].

5.2 Imaging applications

Usually, to monitor the drug delivery to the targeted site, researchers integrate fluorescent dye onto the nanocarrier. But, this technique is hindered by certain limitations, including disruption of the structure of the carrier, burst release of the drug due to the unstable construct, etc. [103]. Hence, aggregation-induced emission (AIE) based fluorophores integrated onto nanocarriers are being constructed widely [104]. Lu and team synthesized a particular DNA sequence to serve as a pH-sensitive nanocluster (iron oxide) assembly, which facilitates the enhancement effect of a contrast agent to distinguish between target and normal tissues. This can even detect small hepatocellular carcinoma cells in their premature period. In an acidic pH atmosphere, the ultra-small iron oxide-based nanocluster disassembles where T2 contrast agent converts to the T1 contrast agent. They concluded that this could serve as a novel contrast agent for MRI [105]. Tan *et al.* fabricated pH-sensitive nanohybrid material for the imaging of pH changes in the dentin region. The construct is tested over an *ex vivo* model to determine the cariogenic substances/ agents. The nanohybrid material gives out two different fluorescence with inversely proportional intensities. The signal thus provided was used to study the cariogenic determinants [106]. Ding *et al.* reported a pH-sensitive nanohybrid material for the targeted detection of cancer cells. They synthesized chitosan/ PEG nanodot decorated with folate receptors for targeted binding and loaded with conjugated oligoelectrolyte-polyhedral oligomeric silsesquioxane for nucleus imaging. The chitosan here acted as the pH-sensitive polymer. The

nanodot delivered the payload in lysosomes. The *in vitro* evaluation involves a breast cancer cell line for the study as it overexpresses folic acid. The uptake of the particle and their localization was studied using confocal laser scanning microscopy. This study was concluded as the simple strategy for the preparation of pH responsive nanomaterials for the detection of cancer cells [107].

5.3 Theranostic applications

As the nanocarrier modified with the pH-responsive polymer can target and deliver payloads, including drugs, siRNA, and various imaging agents, they serve as an efficient theranostic tool in the field of medicine (Table 3). They are majorly being used in cancer theranostics, but they can also monitor the drug release in other disease conditions also. Theodosiou and co-workers synthesized gold nanoparticles modified with polymeric nanocontainers for drug delivery and monitoring them simultaneously. The cellular uptake and localization were compared between the gold nanocontainers and the newly synthesized gold nanoparticle-citrate capped. They observed a sustained release of the drug dox in the acidic environment. The *in vitro* studies were carried out in breast cancer cells. They concluded that the modified nanocontainer with gold nanoparticles delivered the drug at the nucleus, where the site of action of dox is more, which was monitored through confocal laser scanning microscopy. Hence, the study provides a theranostics approach to deliver anticancer agents and monitor the same [108]. Saha *et al.* synthesized a triangular nanoplate with Eu: Gd_2O_3 through the solvothermal method. The nanoplates were coated with polyacrylate via the one-step method and conjugation chemistry. Further, the construct was decorated with folate receptors as a targeting agent in low density in order to deliver the drug in the nucleus. The particle was attached with a free thiol to bind drugs: daunorubicin and curcumin. The developed particle delivered the drug to the nucleus, and also produced fluorescence, which was monitored by MRI technique. The study hence demonstrated novel synthetic nanoplates as a theranostic agent with high cytotoxic effects to cancer cells and biomonitoring of the same [109].

Table 3. Compilation of pH-sensitive polymer for theranostic applications.

Sl. No	Nanoparticle	Surface modification	Contrast agent/ drug	Synthesis strategy	Disease condition	Outcome	Ref.
1.	Gd-doped silicon nanoparticles	Poly (2-diethylamino) ethylmethacrylate) polymer, zeolitic imidazolate framework-8 and folic acid–PEG-maleimide	Dox, chlorine e6	Self-assembly method	Solid tumor	The synthesized nano-carriers exhibited targeted delivery of drug with dual imaging of fluorescence and MR imaging. The *in vitro* study with breast cancer cells showed high cytotoxicity.	[110]
2	Manganese oxide nanoparticles	Poly(acrylic acid)	Methotrexate	-	Invasive ductal carcinoma	Sustained release of drug observed at pH 5.4 with high efficiency and accumulation of cancer tissue than the normal tissue. The *in vitro* MRI results showed that the design developed as a potential diagnostic agent.	[111]
3.	Polysaccharide-based nanomicelles	PEGlyation	Indocyanine green	Self-assembly, alkyl modification, and electrostatic interaction	Breast cancer	The polymer conjugates micelle has a greater encapsulation effect, which increased the photostability of ICG. The leakage was lowered and induced hyperthermic effect.	[59]
4.	PDPL micelle	-	SPIONS/ Paclitaxel	Self-assembly	Hepatocellular carcinoma	The CA-Drug loaded micelle was delivered to the tumor site and visualized by MR imaging. The particle induced cell apoptosis and provided chemotherapeutic effect and MR imaging	[112]
5.	Mesoporous silica-chitosan-gold nanoparticles	Aptamer	Curcumin	-	MUC-1 positive tumor cells	The synthesized nano-system was used to trace a specific biomarker and act as non-invasive imaging for targeted cancer therapy and monitoring.	[113]
6.	PEGylated PLGA nanoparticles	brain metastatic breast cancer cell	Dox	Nano-precipitation method	Brain-metastatic-breast cancer	The formulation shows ability to cross and BBB with high accumulation and extended circulation half-life. It also exhibits cytotoxicity when tested *in vitro* and *in vivo*	[114]

Table 3. (continued).

Sl. No.	Nanoparticle	Surface modification	Contrast agent/ drug	Synthesis strategy	Disease condition	Outcome	Ref.
7.	Iron-gallic acid-based nanoparticle	PEG/PLGA	Gallic acid	-	Breast cancer	This serves as an efficient theragnostic model for accurately detecting the tumor size and location through T_1 MRI contrast. These block copolymers released the drug at the tumor environment and induced apoptosis.	[115]
8.	Polymeric micelles	-	indocyanine green	Sonication method	Lung cancer	The developed nanoplatform provided fluorescence image-guided photothermal therapy. The particle was ultra-pH sensitive and exhibited superior tumor-to-normal tissue contrast. This provided precise information about the tumor's location and size.	[116]
9.	polymer nanoparticles	Cell-penetrating peptides, Calcium phosphate, and aptamers	siRNA and hydroxy-camptothecine	Nano-precipitation method	Breast cancer	The experiment was designed to provide image-guided dual therapy for cancer. The *in vitro* study result showed better therapeutic efficiency than monotherapy. The drug and the siRNA were delivered in the precise location, thus providing gene therapy and chemotherapy.	[117]
10.	MIL-53(Fe)- metal–organic framework	Polydopamine	Camptothecin	-	Breast cancer	The prepared particle exhibited high stability and pH responsive release of payload. The *in vitro* results showed high cellular toxicity, and the *in vivo* study with zebrafish showed excellent anticancer properties. Thus, the theranostic particle was capable of MRI-guided chemotherapy.	[118]

Conclusion and future perspective

The release of cargo mediated by pH responsiveness is a major discussion for designing an effective therapeutic agent. The synthesis can be carried out by three techniques based on the applications: acid-labile linkers, cleavable crosslinkers, or charge-shifting polymers. Modification of nanocarriers through these strategies enables site-specific cargo release by eliminating other adverse effects. The payload will also be protected from leakage or delivery at undesirable locations. Despite the growing interest in pH responsiveness carrier systems, there are very few products under clinical trials. Issues such as biodistribution still require to be improved as, without the targeting ligands, it is not easy for the carriers to reach the target site, and binding them could enable better intracellular delivery. When it comes to the selection of ligands, one has to be very careful about their impact on endosomal acidification. The choice of surface modifiers must not affect the endosomal escape pathway. This is the reason that the folate receptors are not a favorable choice for pH-triggered drug release, as they undergo endocytosis even in neutral pH conditions. Besides this, general ongoing research about the fate of nanoparticles must also be concluded to use them *in vivo*. By addressing minor limitations in the design, the pH-mediated release of drugs can become a powerful strategy to acquire better therapeutic results. Deep investigations are required in the future to improve the specificity of delivery and to extend its application into clinical use. A crucial understanding is required to explore the mechanism of binding between polymer and drug, particle, and the target site. Further studies with *in vivo* models need to be performed to evaluate the toxicity profile of such polymers in the biological environment. This sort of information will provide detailed insight and extended applications. This review discussed the synthesis strategy and recent research investigation that majorly focuses on cancer theranostics.

Acknowledgements

Authors acknowledge CARE for financial and infrastructural support. KH acknowledge CARE for fellowships.

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