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Short Review Article

A Review on pH and Temperature Responsive Gels in Drug Delivery

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Abstract:
Anticancer drugs play important roles in cancer treatment. However, these drugs have many disadvantages such as poor solubility, high toxicity, and serious side effects like hair loss, nausea and vomiting, anemia etc. To overcome these drawbacks, many attempts have been made to develop novel controlled drug delivery systems. They can encapsulate the drug and release it to the cancer site without leaking into other sites. The employment of multi-responsive hydrogels as a drug delivery system have some advantages over other drug delivery systems due to their ease of preparation, high efficiency, high-water content, tunable physical, and biological properties. The most advantages of these hydrogels is the volume phase transitions in their cross-linked three-dimensional networks as exposure to external stimuli such as temperature, pH, pressure, electric field, magnetic field and light. There has been research on other drug delivery systems which can respond to changes in pH and temperature for targeted drug release. Among those, gels have been studied mostly for their dual responsiveness. This provides an update on progress of gel based dual pH and temperature responsive drug delivery systems. Various systems under these categories for targeted and controlled delivery of different classes of drugs such as ant diabetic and antibiotic drugs with special emphasis on anticancer drugs are discussed in this review.

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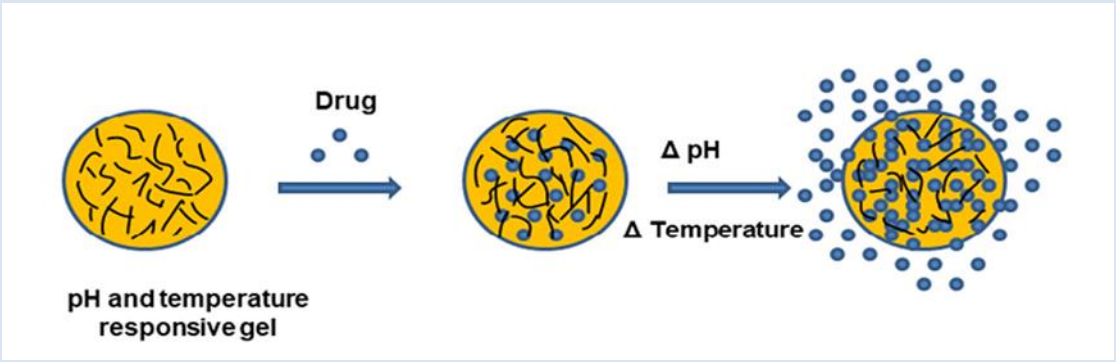
Keywords: Dual responsive; Hydrogels; Nanogels; Microgels

Graphical Abstract:



Biography:

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1. Introduction

In recent years drug formulation research, one of the main focus or challenge has been as how has been the focus of many research studies to assure the safety of drug carriers to the human body with good biocompatibility and non-toxic side effects [1]. With recent advancements in drug delivery technology, several nanoparticulate drug delivery systems (NDDS) have been designed to deliver their payload specifically at the target site. Some of the nanoparticulate delivery systems/carriers include liposomes [2], polymeric micelles [3], polymeric nanoparticles [4], gold [5], silver [6], silica [7] and other metal nanoparticles.
Among various stimuli, pH and temperature are the primary choice, as they are simple to understand [8]. Any imbalance in body pH or temperature may alter immune response and lead to autoimmune diseases, infectious diseases, cancer, and diabetes, Parkinson's disease. Also changes in the pH of the body fluids may sometimes cause serious conditions such as metabolic acidosis or alkalosis where pH of body fluids is decreased or increased, respectively. In lactic acidosis and chlorine alkalosis there is a change in pH of the body fluids from the normal physiological pH [9-12].

This concept has stimulated researchers towards the development of thermo and pH dual stimuli-responsive polymeric nanomaterials for cancer treatment [13-15].

Polymeric micelles and polymeric nanoparticles are the extensively studied systems for pH and temperature responsiveness. The aim of this review is to provide an update on progress of gel based dual pH and temperature responsive drug delivery systems and other systems such as dendrimers, membranes, liposomes, microcapsules and microspheres.

2. Dual pH and Temperature Responsive Drug Delivery Systems

2.1. Gels

Gels are three dimensional arrays containing medicinal, cosmetic or other agents with size varying from 1 nm to 1 mm. Pharmaceutical gels exhibit swelling ability, stability, and biocompatibility that cause no irritation to patient and therefore regarded as reliable drug delivery systems [16]. They can be designed to exhibit significant volume changes in response to small changes in their environment such as pH, temperature, ionic strength, electric potential, salt concentration, light, ultrasonic sound, electric current, electric magnetic field, and biomolecules, to control rate of drug release [16-18]. Intravenous gel formulations can form an in-situ gel to release the desired drug depending on the levels of pH and temperature [16]. Gels can be prepared from various natural polysaccharides which include salep, heparin, alginic acid, hyaluronic acid, chitosan, and dextran. These polysaccharides can be chemically modified so that they can be responsive to external or internal stimuli [13]. Due to their release characteristics, gels can encapsulate agents such as drugs and release at the desired target site. Some gels could have growth factors, and fillers to provide repair on specific areas [20].

2.2. Hydrogels

Hydrogels are cohesively held three-dimensional polymer webs which exhibit certain pH and temperature sensitive responses when prepared using stimuli responsive polymers. Sensitivity to pH and temperature can be beneficial in drug delivery systems as it gives hydrogels the ability to specifically releasemedication where appropriate range of pH or temperature is desired [21-23]. Till date, various polymers such as xylan, poly(N- isopropylacrylamide) (PNIPAM)/carboxymethyl chitosan, β-CD-conjugated poly(ε-lysine) (βCDPL) and 3-trimethylsilylpropionic acid, poly [N,N- dimethyl aminoethyl methacrylate-co-poly(poly(ethylene glycol) methyl ether methacrylate] [poly(DMAEMA-co-MPEGMA)], β-cyclodextrin, 2-methylacrylic acid and N,N'-methylene diacrylamide have been used for preparing hydrogels [1].

2.3. Microgels

Microgels are macromolecular colloidal gels comprised of three-dimensional polymeric network crosslinked via chemical bonds. They are polymeric gel particles in the size range of micrometers uniformly dispersed in a solvent mediumand have swelling properties [24-26].
Hydrogels have been widely investigated for facilitating the controlled release of a variety of

clinically-relevant drugs [27-35]. Hydrogels have found particular utility in the area of controlled release since they can be loaded with high fractions of drugs due to their high internal free volume and can be fabricated to have similar physical, mechanical, and chemical properties to native extracellular matrix, which generally results in high biocompatibility in a variety of biological environments [26-29]. However, traditional hydrogels suffer from two key limitations to their facile use in biological applications: (1) their high elasticity coupled with their macroscopic dimensions make them difficult to administer via injection, instead requiring surgical insertion [27]; (2) the highly hydrated microstructure results in poor uptake of hydrophobic drugs [36] and rapid release of hydrophilic drugs [27, 37], limiting both the types and the rates of drug release that are possible from hydrogel based systems. While a range of physical self-assembly approaches [29,38-40] and several rapid covalent bond forming chemistries compatible with physiological conditions [31,41-43] have been developed to facilitate inject ability, the long-term release of hydrophilic drugs remains a challenge, with few formulations reported to achieve release durations for greater than 1 month [37].

In order to address this problem, a range of multi-phase, ‘‘plum pudding’’ hydrogels have been developed in which a variety of nano- or micron-sized drug carriers (e.g. liposomes [44], polymer nanoparticles [45], polymer microparticles [46], and microgels [47-50]) are physically entrapped inside hydrogels. Relative to single phase bulk hydrogels, multi-phase hydrogels can introduce affinity sites that facilitate increased loading of a target drug [51] as well as additional diffusive and/or partitioning barriers to tune the release of that drug through the bulk hydrogel phase [52-54]. For example, the burst effect often seen in microgel-based drug release could be mitigated in a composite hydrogel system [54, 55]. Relative to the use of the drug carriers alone, the hydrogel can immobilize the nanocarrier at the injection site to facilitate local drug delivery [27, 56] and mask any potential immune or inflammatory reactions to the nanocarrier [57].

Microgel–hydrogel nanocomposites have particular advantages for the delivery of water-soluble drugs. Given that both phases of a microgel–hydrogel nanocomposite are hydrogel-based, these materials offer the unique potential to independently engineer both the hydrogel and microgel phase to optimize the drug release profile through the use of differential drug partitioning [58] or cross-linking [59] between the two gel phases. In addition, the degree of swelling of both hydrogel-based phases can be tuned to dynamically create internal stresses or free volume [50, 59-62] within the soft nanocomposite system, offering the potential for on-demand control over both drug partitioning and drug diffusion over the course of drug release.

Nigro *et al.* [63], characterized the local structure of the dual responsive interpenetrated polymer network microgels at different pH and temperatures. These microgels were prepared via radical polymerization using NIPAM, acrylic acid and N, N`-methylene-bis-acrylamide (BIS). Microgels exhibited structural changes with variations in pH and temperature. Increasing the temperature resulted in formation of a microgel with porous solid structure from a microgel with inhomogeneous interpenetrated polymer network. Bardajee *et .al* [64], prepared iron oxide nanocomposite nanogel based on poly (N-isopropylacrylamide)-co-(2-dimethylamino ethyl methacrylate) grafted onto sodium alginate, as a biocompatible polymer and iron oxide nanoparticles as nanometer base (PND/ION-NG). Then it added into the solution of poly (2-dimethylamino ethyl methacrylate) grafted onto sodium alginate. Through dropwise addition of mixed aqueous solution of iron salts into the prepared polymeric solution, a novel hydrogel nanocomposite with excellent pH, thermo, and magnetic responsive was fabricated. The synthesized samples were fully characterized by using Fourier transform infrared (FT-IR) spectroscopy , thermal gravimetric analysis (TGA), scanning electron microscopy with energy dispersive X-ray (SEM-EDS) analysis, vibrating sample magnetometer and atomic force microscopy, and a mechanism for PNIPAM-co-PDMA)/NaAlg-ION nanogel-PDMA/NaAlg-ION-hydrogel and PNIPAM-co-PDMA)/NaAlg-ION nanogel formation was suggested. The release rate of doxorubicin hydrochloride (DOX) as an anticancer drug was studied at different pHs and temperatures in the presence and absence of magnet. The results revealed that the aforementioned factors have a great impact on drug release from this nanocomposite. The result showed that DOX release could be sustained for up to 12.5 days from these nanocomposite hydrogels, significantly longer than that achievable using the constituent hydrogel or nanogel alone (<1 day).

Bardajee *et al* [65] have prepared poly [(N-isopropylacrylamide)-co-(2-dimethylamino ethyl methacrylate) nanogel by copolymerization processes and then added it into the solution of poly (2-dimethylamino ethyl methacrylate)] grafted onto salep. Through dropwise addition of mixed aqueous solution of iron salts into the prepared polymeric solution, a novel hydrogel nanocomposite with pH, thermo, and magnetic responsive was fabricated. The obtained hydrogel nanocomposites were characterized by FT-IR spectroscopy, TGA, X-ray diffraction (XRD), SEM, vibrating sample magnetometer, and atomic force micrographs (AFM). The dependence of swelling properties of hydrogel nanocomposite on the

temperature, pH, and magnetic field were investigated. The release behavior of doxorubicin hydrochloride (DOX) drug from DOX loaded into the synthesized hydrogel nanocomposite was investigated at different pHs, temperatures, and magnetic field. In addition, the drug release behavior from obtained hydrogel nanocomposite was monitored via different kinetic models. Lastly, the toxicity of the DOX and DOX-loaded hydrogel nanocomposite were studied on MCF-7 cells at different times. The results demonstrated that the PAN-nanogel-PAS-Fe_3O_4 NPs hydrogel nanocomposite had not any cytotoxicity on MCF-7 at various times. In contrast, DOX had a relatively high toxicity on MCF-7 cells. However, the results of the experiments showed that the toxicity of DOX was reduced after its encapsulating in the PANnanogel-PAS-Fe_3O_4 NPs hydrogel nanocomposite. The release experiments showed that the release of DOX drug was accelerated at pH 5.3 with temperature environment 42 °C. In addition, the results of the cytotoxicity test indicate that the toxicity of DOX after its embedding into the hydrogel nanocomposite significantly decreased. These results suggested that the obtained hydrogel nanocomposite might have high potential applications in drug delivery systems.

Sivakumaran *et al* [66] have researched on Soft nanocomposite hydrogels consisting of thermo responsive microgels physically entrapped or covalently cross-linked to a non-thermo responsive hydrogel are synthesized and tested for their capacity to facilitate long-term drug release of a small molecule drug. Copolymer microgels based on N-isopropylacrylamide and acrylic acid were synthesized that exhibited ionic affinity for binding to bupivacaine, a cationic local anesthetic. These microgels were subsequently physically entrapped within an in situ-gelling carbohydrate-based hydrogel network cross-linked via hydrazide–aldehyde chemistry; alternately, hydrazide-functionalized microgels were prepared that covalently cross-linked to the bulk hydrogel phase. Both the overall rate of drug release and the magnitude of the burst release were significantly decreased when microgels were restricted from undergoing a phase transition between the preparation temperature of the nanocomposite (25 ˚C) and the test temperature (37 ˚C), whether deswelling was inhibited by increasing the cross-link density within the microgel itself or by cross-linking the microgel to the bulk hydrogel network. This result facilitates facile tuning of soft nanocomposite drug delivery systems to achieve targeted drug release kinetics.

Sivakumaran *et al* [67] have investigated the design and application of soft nanocomposite injectable hydrogels containing entrapped microgels for small molecule drug delivery is demonstrated. Copolymer microgels based on N-isopropylacrylamide and acrylic acid exhibited both ionic and hydrophobic affinity for binding to bupivacaine, a cationic local anesthetic used as a model drug. Microgels were subsequently immobilized within an in situ-gelling hydrogel network cross-linked via hydrazide-aldehyde chemistry to generate hydrogel−microgel soft nanocomposites. Drug release could be sustained for up to 60 days from these nanocomposite hydrogels, significantly longer than that achievable using the constituent hydrogel or microgels alone (<1 week). Drug release kinetics could be readily tuned by varying the affinity of the microgel and hydrogel phases for drug−polymer interactions and the network density of the hydrogel phase.

The binding of polyelectrolyte to a temperature and pH-responsive microgel based on poly-N-isopropylacrylamide (PNiPAM) copolymerized with methacrylic acid (MAA) as a soft and porous substrate was investigated as a function of time and temperature in order to probe rearrangements in such complexes. Oppositely charged polyelectrolytes bind to the charged microgels, and the composition of the resulting complexes stays constant with time. The number of titrable COOH groups, the size, and the electrophoretic mobility of the complexes, however, change with time due to rearrangements of polyelectrolyte chains inside of the microgel. Polyelectrolytes can be used to modify the properties of microgels. The volume phase transition temperature (VPTT) of PNiPAM-co-MAA microgels depends on the pH value, while microgel polyelectrolyte complexes collapse above the VPTT of 32 ˚C independently of the pH value. The experiments reveal that polyelectrolytes can be partially released from microgel-polyelectrolyte complexes at T> VPTT. In addition, rearrangements are induced by the collapse. Rebinding of the polyelectrolyte occurs upon reswelling of the complex when the temperature is reduced below the VPTT. Such temperature cycles affect the size and electrophoretic mobility of complexes. The rearrangements can be used to increase the amount of polyelectrolyte that is bound to the microgel and are thus important for applications that rely on loading microgels with polymers. Interestingly, the colloidal stability of the complexes at T>VPTT depends on the preparation temperature; complexes prepared at T< VPTT remain colloidally stable when heated to T>VPTT; on the other hand, complexes prepared at T> VPTT display poor colloidal stability [68].

Jochen *et .al* [69] have assessed two sets of core-shell microgels composed of temperature-sensitive poly(N-isopropylacrylamide) (PNiPAM) with different spatial distribution of pH-sensitive methacrylic acid (MAA) groups were prepared. The cores consist of either PNiPAM (neutral core; nc) or PNiPAM-co-MAA (charged core; cc). A charged shell existing of PNiPAM-co-MAA was added to the neutral core

(yielding neutral core-charged shell; nccs), on the charged core, on the other hand, a neutral shell of PNiPAM was added (charged core-neutral shell; ccns). Complexes of these microgels with positively charged poly (diallyl dimethyl ammonium chloride) (PDADMAC) of different molar masses were prepared. The amount of bound polyelectrolyte was quantified, and the microgel-polyelectrolyte complexes were characterized with respect to electrophoretic mobility and hydrodynamic radius. The penetration of polyelectrolyte into the microgel was also monitored by means of lifetime analysis of a fluorescent dye covalently bound to poly(L-lysine) providing information on the probe's local environment. The architecture of the microgel has a significant influence on the interaction with oppositely charged polyelectrolyte. Complexes with microgel with the charged shell tend to flocculate at charge ratios of 1 and are thus similar to polyelectrolyte complexes with rigid colloidal particles. Complexes with microgels that consist of a charged core and a neutral shell show very different properties: They are still temperature sensitive and reveal an influence of the polyelectrolyte's chain length. Low molecular weight PDADMAC can penetrate through the neutral shell into the charged core, and thus nearly no charge reversal occurs. The high-MW polyelectrolyte does not penetrate fully and leads to charge reversal. The results demonstrate that microgels are able to absorb or adsorb polyelectrolytes depending on the polyelectrolyte's chain length and the microgels architecture. Complexes with different surface properties and different colloidal stability can be prepared, and polyelectrolytes can be encapsulated in the microgel core. Thus, multisensitive core-shell microgels combine permeability and compartmentalization on a nanometer length scale and provide unique opportunities for applications in controlled uptake and release.

Swen *et .al* [70] have studied the thermo sensitive composite hydrogels that consist of a poly(acrylamide) hydrogel matrix with embedded micrometer-sized poly(N-isopropylacrylamide) microgel beads are promising models for complex, heterogeneous gels. This project has been reviewed of the microgel beads coupling with the hydrogel matrix and the formation of interpenetrating networks inside the microgels by confocal two-focus fluorescence correlation spectroscopy (2fFCS). This technique serves to study the effects of the heterogeneous structure of the composite hydrogels on the diffusive mobility of nanoscopic dextran tracers within the gels. Our investigations revealed that, formation of interpenetrating networks inside the embedded microgel beads depends on their cross-link density, whereas interpenetrating networks are formed inside the weakly cross-linked beads and they are not formed inside the strongly crosslinked beads. If the formation of interpenetrating networks occurs, the temperature-dependent swelling and deswelling of the beads is obstructed. In addition, the mobility of dextran tracers inside the embedded microgel beads is hindered compared to those in free beads and in the surrounding gel matrix. Surprisingly, the surrounding poly (acrylamide) hydrogel matrix swells in homogeneously when the embedded poly (N-isopropylacrylamide) beads collapse upon heating. This indicates the formation of pores near the surface of the collapsed beads, offering promising means to tailor composite hydrogels for applications as membranes with tunable permeability. Our experiments also demonstrate the utility of 2fFCS to study spatially resolved diffusion in complex environments, which is of great interest in biomaterials research.

Karnoosh-Yamchi and colleagues prepared insulin loaded pH responsive nanogels using NIPAAm-MAA-HEM polymers via radical polymerization technique and were tested at two different pHs i.e., 1.2 and 6.8. At pH of 1.2, nanogels were able to stay afloat in 100 mL of PBS, whereas at pH of 6.8, nanogels were able to stay afloat in 100 mL of HCl. Samples analyzed from the nanogels in both PBS and HCl solutions showed that insulin release from nanogels was high in pH 6.8, and low in acidic environments. Thus, pH responsive insulin loaded nanogels can be considered as a potential candidate for oral insulin therapy [71]. Interpenetrating polymeric nanogels were prepared using biocompatible gelatin macromolecules and poly (acrylamidoglycolic) acid using free radical emulsion polymerization technique. These nanogels were further loaded with curcumin to evaluate anticancer activity. pH sensitive curcumin loaded nanogels were readily dissolved in aqueous solutions with EE% ranging from 42% to 48%. Cytotoxicity studies performed in human dermal fibroblast cells have shown that nanogels were highly biocompatible with cell viability ranging from 97% to 100%. In addition, curcumin loaded nanogels showed superior anticancer activity against colorectal cancer cell line compared to free curcumin. This study has concluded that curcumin loaded IPN nanogels may be used for colorectal cancer treatment [72].

Xiong *et al.* [73], prepared pH and temperature sensitive poly (NIPAM-co-acrylic acid) nanogels loaded with doxorubicin. Nanogels were spherical (380 nm) at 20 ˚C and when the temperature was increased to 37 ˚C, nanogels collapsed to irregular shapes with a diameter of 60 nm (Figure 1). Change in the shape of nanogels was due to the transition from hydrophilicity to hydrophobicity. Moreover, nanogels also appearedto be pH sensitive; as the lower critical solution temperature (LCST) increased to 50 ˚C, 43 ˚C, and 41 ˚C with increasing the pH up to 7.4, 6.8, and 5.3, respectively. Rapid release of doxorubicin was

observed at low pH compared to high pH (70% at 150 h for pH 5.3 versus <20% at 150h for pH 6.8 and 7.4). Blank nanogels were non-toxic as cell viability was more than 90%. Anticancer activity of doxorubicin loaded nanogels was slightly higher compared to free doxorubicin without any impact of changes in temperature or pH. Although this study proved the dual responsiveness of nanogels at different pH and temperatures, it lacked in evaluating the effect of higher temperatures (>37 ˚C, usually observed during infections) on the release of doxorubicin.

Peng and colleagues prepared pH and temperature sensitive nanogels (130 nm to 250 nm) loaded with cisplatin using NIPAM and methyl ether methacrylate via emulsion polymerization [74]. Nanogels displayed slow release of cisplatin at 37 ˚C versus 25 ˚C (room temperature). Furthermore, cisplatin release from the nanogels was 50%, 65% and 80% at pH 7.38, 6.0 and 5.0, respectively. Cytotoxicity of cisplatin loaded nanogels was low compared to free cisplatin against MCF-7 and Hela cells due to controlled release with nanogels. Whereas, in A549 cells, cisplatin loaded nanogels were highly toxic compared to free cisplatin. In vivo pharmacokinetic studies in mice revealed longer circulation time with nanogels compared to free doxorubicin. The peak plasma concentration was 26.10 ± 10.98 mg/mL and 41.07 ± 12.20 mg/mL, with free cisplatin and cisplatin loaded nanogels respectively. The area under the curve (AUC 0~α) was 44.23 ± 18.67 mg.h/mL and 121.31 ± 32.33 mg.h/mL for free cisplatin and cisplatin-loaded nanogels, respectively. In vivo anticancer activity in mice was also better with nanogels compared to free cisplatin with reduced adverse effects associated with cisplatin therapy. Results suggested that, doxorubicin loaded nanogels could be a potential drug delivery system in treatment of cancer in vivo. It would be great to understand the purpose of carrying drug release study at room temperature and its clinical significance. Preparation of smart nanogels has also been reported with other polymers such as N-vinyl caprolactam (VCL), acrylamidoglycolic acid (AGA) [75] and poly (vinylcaprolactam-co-2-dimethylaminoethyl metha-crylate) [P (VCL-co-DMAEMA)] [76]. Nanogel developed demonstrated responsiveness to changes in pH and temperature for drug release.

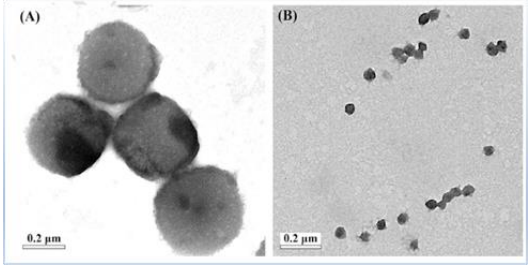

Figure 1. Micro-morphology of DOX-PNA nanogels at (A) 20 ◦C and (B) 37 ◦C respectively. Reproduced from [69].

Very recently, salep modified graphene oxide was used as a capping agent in preparation of nanogels prepared using PNIPAM and acrylic acid. Salep, a polysaccharide obtained from tubers and was used as a reducing agent. Nanogels were spherical and uniformly distributed with an average size of 82 nm. In vitro drug release studies showed that the nanogels exhibited sustained and faster release of doxorubicin in acidic conditions (pH=5.0) and high temperature (42 ˚C) compared with physiologic conditions. Cytotoxicity studies in HeLa cells revealed that doxorubicin loaded nanogels showed superior cytotoxicity compared with free doxorubicin [77]. Zhou *et al*., synthesized a novel crosslinker containing three vinyl groups and co-polymerized with NIPAM to prepare novel nanogel sensitive to pH and temperature. Prepared nanogels with different concentrations of the crosslinker have shown shrinking properties at low pH (1-7) and swelling properties at increasing temperatures (25 ˚C-37 ˚C) [78]. Although, nanogels reported in this section exhibited dual responsiveness to pH and temperature, majority of the studies were limited to in vitro characterization. It would be interesting to evaluate the efficacy and toxicity of these promising drug delivery systems in animal models.

3. Conclusion and Future Perspectives

Drug delivery systems implemented with pH and temperature sensitivity have been developed for enhanced site specificity and controlled drug release profiles. These systems also exhibited enhanced mechanical properties that were attributed with conjugated polymeric materials ensuring that payload delivery even when induced to high stress or strain conditions. Biocompatibility of the developed drug delivery systems proved to be viable for biological systems exhibiting good levels of cell viability. Thus, these novel drug delivery systems with dual responsiveness capabilities have proved to be viable systems for enhanced drug delivery and candidates for further research. Scientists have been successful in synthesizing/formulating different drug delivery systems with sensitivity to both pH and temperature with promising in vitro results for high efficacy. However, very few studies have been conducted in animal models to confirm the results in vivo. For effective translation into clinical practice, these systems further need to be studied in depth using in vivo techniques. Moreover, majority of the formulations were mainly limited to exploring the loading of anticancer drugs such as doxorubicin and paclitaxel. Therefore, there is a need to explore the novel dual responsive systems with in -vivo and in -vitro studies that are not only limited to cancer but other diseases such as diabetes, infectious diseases, and

autoimmune diseases to ensure the efficacy of the drug delivery system with various disease treatments.

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Disclosure statement

No potential conflict of interest was reported by the authors.

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