A Review on pH and Temperature Responsive Gels in Drug Delivery

Ghasem Rezanejade Bardajee\textsuperscript{a,}* , Somayeh Ghavami\textsuperscript{a}, Samaneh Sadat Hosseini\textsuperscript{a,b}

\textsuperscript{a} Department of Chemistry, Payame Noor University, P.O. Box 19395-3697, Tehran, Iran
\textsuperscript{b} Faculty of Chemistry, Shahrood University of Technology, P.O. Box 316, Shahrood, Iran

Received Date: 06 October 2019, Revise Date: 10 December 2019, Accept Date: 13 December 2019

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.

DOI: 10.33945/SAMI/JCR.2020.2.1

Keywords: Dual responsive; Hydrogels; Nanogels; Microgels

Graphical Abstract:

Biography:

Ghasem Rezanejade Bardajee: He Received his Ph.D. degree in Chemistry from Sharif University of Technology. He is currently a professor at the faculty of chemistry of the Payame Noor University (Iran). His research encompasses the sensitive nanocomposite hydrogels, green chemistry, drug delivery, quantum dots, and solar cells.

*Corresponding author: Ghasem Rezanejade Bardajee, Email: rezanejad@pmu.ac.ir
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 saperl, 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 release medication 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-copoly(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 medium and 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.

Negro 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. Bardjee 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). Bardjee 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$_3$O$_4$ 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$_3$O$_4$ NPs hydrogel nanocomposite. The release experiments showed that the release of DOX drug was accelerated at pH 5.3 with temperature environment 42 ºC. 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 ºC) and the test temperature (37 ºC), 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 ºC 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 colloidal 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
The microgels by as also monitored showed of the weakly cross investigations revealed that, formation of nanoscopic dextran tracers within the gels. Composite hydrogels on the diffusive mobility of spectroscopy (2fFCS). This technique serves to study confocal two interpenetrating networks inside the embedded microgel 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 appeared to 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 ethyl 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 for free doxorubicin 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 methacrylate) [P (VCL-co-DMAEMA)] [76]. Nanogel developed demonstrated responsiveness to changes in pH and temperature for drug release.

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.

Acknowledgment
The Authors are grateful to PNU for financial support

Disclosure statement
No potential conflict of interest was reported by the authors.

References
[1] Luo, Y. L., Zhang, X. Y., Fu, J. Y., Xu, F., & Chen, Y. S. (2017). Novel temperature and pH dual-sensitive PNI.PAM/CMCS/MWCNT semi-IPN nanohybrid hydrogels: Synthesis, characterization, and DOX drug release. International Journal of Polymeric Materials and Polymeric Biomaterials, 66(8), 398-409

[2] Daraee, H., Etemadi, A., Kouhi, M., Alimirzalou, S., & Akbarzadeh, A. (2016). Application of liposomes in medicine and drug delivery. Artificial cells, nanomedicine, and biotechnology, 44(1), 381-391.

[3] Biswas, S., Kumari, P., Lakhanvi, P. M., & Ghosh, B. (2016). Recent advances in polymeric micelles for anti-cancer drug delivery. European Journal of Pharmaceutical Sciences, 83, 184-202.

[4] Masood, F. (2016). Polymeric nanoparticles for targeted drug delivery system for cancer therapy. Materials Science and Engineering: C, 60, 569-578.

[5] Bardajee, G. R., Mizani, F., & Hosseini, S. S. (2017). pH sensitive release of doxorubicin anticancer drug from gold nanocomposite hydrogel based on poly (acrylic acid) grafted onto salep biopolymer. Journal of Polymer Research, 24(3), 48.

[6] Kumar, C. G., & Poornachandra, Y. (2015). Biodegraded synthesis of Miconazole-conjugated bacterial silver nanoparticles and their application as antifungal agents and drug delivery vehicles. Colloids and Surfaces B: Biointerfaces, 125, 110-119.

[7] Wen, J., Yang, K., Liu, F., Li, H., Xu, Y., & Sun, S. (2017). Diverse gatekeepers for mesoporous silica nanoparticles based drug delivery systems. Chemical Society Reviews, 46(19), 6024-6045.

[8] Davaran, S., Ghamkhari, A., Alizadeh, E., Massoumi, B., & Jaymand, M. (2017). Novel dual stimuli-responsive ABC triblock copolymer: RAFT synthesis, “schizophrenic” micellization, and its performance as an anticancer drug delivery nanosystem. Journal of colloid and interface science, 488, 282-293.

[9] Kellum, J. A. (2000). Determinants of blood pH in health and disease. Critical Care, 4(1), 6.

[10] Hanson, D. F. (1997). Fever, temperature, and the immune response. Annals of the New York Academy of Sciences, 813(1), 453-464.

[11] Carlin, K. (2014). Autoimmune disease pH and temperature. Journal of clinical medicine research, 6(4), 305-307.

[12] Cao, Z., Liu, L., & Wang, J. (2010). Effects of pH and Temperature on the Structural and Thermodynamic Character of a-syn12 Peptide in Aqueous Solution. Journal of Biomolecular Structure and Dynamics, 28(3), 343-353.

[13] Bhattacharya, D., Behera, B., Sahu, S. K., Ananthakrishnan, R., Maiti, T. K., & Pramanik, P. (2016). Design of dual stimuli responsive polymer modified magnetic nanoparticles for targeted anti-cancer drug delivery and enhanced MR imaging. New Journal of Chemistry, 40(1), 545-557.

[14] Zhang, L., Guo, R., Yang, M., Jiang, X., & Liu, B. (2007). Thermo and pH dual-responsive nanoparticles for anti-cancer drug delivery. Advanced Materials, 19(19), 2988-2992.

[15] Soppimath, K. S., Tan, D. W., & Yang, Y. Y. (2005). pH-triggered thermally responsive polymer core–shell nanoparticles for drug delivery. Advanced materials, 17(3), 318-323.

[16] Singh, N. K., & Lee, D. S. (2014). In situ gelling pH-and temperature-sensitive biodegradable block copolymer hydrogels for drug delivery. Journal of controlled release, 193, 214-227.

[17] Soppimath, K. S., Aminabhavi, T. M., Dave, A. M., Kumbar, S. G., & Rudzinski, W. E. (2002). Stimulus-responsive “smart” hydrogels as novel drug delivery systems. Drug development and industrial pharmacy, 28(8), 957-974.

[18] Sood, N., Bhardwaj, A., Mehta, S. S., & Mehta, A. (2016). Stimuli-responsive hydrogels in drug delivery and tissue engineering. Drug delivery, 23(3), 748-770.

[19] Basu, A., Kundur, K. R., Abtew, E., & Domb, A. J. (2015). Polysaccharide-based conjugates for biomedical applications. Biocugnate chemistry, 26(8), 1396-1412.

[20] Thambi, T., Phan, V. G., & Lee, D. S. (2016). Stimuli-Sensitive Injectable Hydrogels Based on Polysaccharides and Their Biomedical Applications. Macromolecular rapid communications, 37(23), 1881-1896.

[21] Choi, H. S., Huh, K. M., Ooya, T., & Yui, N. (2003). pH-and thermosensitive supramolecular assembling system: rapidly responsive properties of β-cyclodextrin-conjugated poly(ε-lysine). Journal of the American Chemical Society, 125(21), 6350-6351.
[22] Eljarart-Binstock, E., Raiskup, F., Stepenksy, D., Domb, A. J., & Frucht-Pery, J. (2004). Delivery of gentamicin to the rabbit eye by drug-loaded hydrogel iontophoresis. Investigative ophthalmology & visual science, 45(8), 2543-2548.

[23] Sun, K., Guo, J., He, Y., Song, P., Xiong, Y., & Wang, R. M. (2016). Fabrication of dual-sensitive keratin-based polymer hydrogels and their controllable release behaviors. Journal of Biomaterials science, Polymer edition, 27(18), 1926-1940.

[24] Plamper, F. A., & Richtering, W. (2017). Functional microgels and microgel systems. Accounts of chemical research, 50(2), 131-140.

[25] Li, Z., & Ngai, T. (2013). Microgel particles at the fluid–fluid interfaces. Nanoscale, 5(4), 1399-1410.

[26] Lopez, V. C., Hadgraft, J., & Snowden, M. J. (2005). The use of colloidal microgels as a (Trans) dermal drug delivery system. International journal of pharmaceutics, 292(1-2), 137-147.

[27] T.R. Hoare, D.S. Kohane, Polymer, 49 (2008) 1993.

[28] Andrade-Vivero, P., Fernandez-Gabriel, E., Alvarez-Lorenzo, C., & Concheiro, A. (2007). Improving the loading and release of NSAIDs from pHEMA hydrogels by copolymerization with functionalized monomers. Journal of pharmaceutical sciences, 96(4), 802-813.

[29] Bos, G. W., Jacobs, J. J., Koten, J. W., Van Tomme, S., Veldhuis, T., van Nostrum, C. F., ... & Hennink, W. E. (2004). In situ crosslinked biodegradable hydrogels loaded with IL 2 are effective tools for local IL-2 therapy. European journal of pharmaceutical sciences, 21(4), 561-567.

[30] Bouhadir, K. H., Kruger, G. M., Lee, K. Y., & Mooney, D. J. (2000). Sustained and controlled release of daunomycin from cross-linked poly (aldehyde guluronate) hydrogels. Journal of pharmaceutical sciences, 89(7), 910-919.

[31] Cai, S., Liu, Y., Shu, X. Z., & Prestwich, G. D. (2005). Injectable glycosaminoglycan hydrogels for controlled release of human basic fibroblast growth factor. Biomaterials, 26(30), 6054-6067.

[32] Cho, K. Y., Chung, T. W., Kim, B. C., Kim, M. K., Lee, J. H., Wee, W. R., & Cho, C. S. (2003). Release of ciprofloxacin from poloxamer-graft-hyaluronic acid hydrogels in vitro. International journal of pharmaceutics, 260(1), 83-91.

[33] Galeska, I., Kim, T. K., Patil, S. D., Bhargwaj, U., Chattopadhyay, D., Papadimitrakopoulos, F., & Burgess, D. J. (2005). Controlled release of dexamethasone from PLGA microspheres embedded within polyacid-containing PVA hydrogels. The AAPS journal, 7(1), E231-E240.

[34] Liu, J., Lin, S., Li, L., & Liu, E. (2005). Release of theophylline from polymer blend hydrogels. International journal of pharmaceutics, 298(1), 117-125.

[35] Nishi, K. K., & Jayakrishnan, A. (2007). Self-Gelling Primaquine— Gum Arabic Conjugate: An Injectable Controlled Delivery System for Primaquine. Biomacromolecules, 8(1), 84-90.

[36] Chen, M. C., Tsai, H. W., Liu, C. T., Peng, S. F., Lai, W. Y., Chen, S. J., ... & Sung, H. W. (2009). A nanoscale drug-entrapment strategy for hydrogel-based systems for the delivery of poorly soluble drugs. Biomaterials, 30(11), 2102-2111.

[37] Kang, G. D., Cheon, S. H., & Song, S. C. (2006). Controlled release of doxorubicin from thermosensitive poly (organophosphazene) hydrogels. International journal of pharmaceutics, 319(1-2), 29-36.

[38] Qiao, M., Chen, D., Ma, X., & Liu, Y. (2005). Injectable biodegradable temperature-responsive PLGA–PEG–PLGA copolymers: synthesis and effect of copolymer composition on the drug release from the copolymer-based hydrogels. International Journal of Pharmaceutics, 294(1-2), 103-112.

[39] Lim, D. W., Nettles, D. L., Setton, L. A., & Chilkoti, A. (2007). Rapid cross-linking of elastin-like polypeptides with (hydroxymethyl) phosphines in aqueous solution. Biomacromolecules, 8(5), 1463-1470.

[40] Chen, P. (2005). Self-assembly of ionic-complementary peptides: a physicochemical viewpoint. Colloids and Surfaces A: Physicochemical and Engineering Aspects, 261(1-3), 3-24.

[41] Ito, T., Yeo, Y., Highley, C. B., Bellas, E., Benitez, C. A., & Kohane, D. S. (2007). The prevention of peritoneal adhesions by in situ cross-linking hydrogels of hyaluronic acid and cellulose derivatives. Biomaterials, 28(6), 975-983.

[42] Luo, Y., Kohler, J. B., Heaton, J. T., Jia, X., Zeitzels, S. M., & Langer, R. (2010). Injectable hyaluronic acid-dextran hydrogels and effects of implantation in ferret vocal fold. Journal of Biomedical Materials Research Part B: Applied Biomaterials, 93(2), 386-393.

[43] Elbert, D. L., Pratt, A. B., Lutolf, M. P., Halstenberg, S., & Hubbell, J. A. (2001). Protein delivery from materials formed by self-selective conjugate addition reactions. Journal of Controlled Release, 76(1-2), 11-25.
[44] Popescu, M. T., Mourtas, S., Pampalakis, G., Antimisiaris, S. G., & Tsitsilianis, C. (2011). pH-responsive hydrogel/liposome soft nanocomposites for tuning drug release. Biomacromolecules, 12(8), 3023-3030.

[45] Baumann, M. D., Kang, C. E., Tator, C. H., & Shoichet, M. S. (2010). Intrathecal delivery of a polymeric nanocomposite hydrogel after spinal cord injury. Biomaterials, 31(30), 7631-7639.

[46] Baumann, M. D., Kang, C. E., Stanwick, J. C., Wang, Y., Kim, H., Lapitsky, Y., & Shoichet, M. S. (2009). An injectable drug delivery platform for sustained combination therapy. Journal of Controlled Release, 138(3), 205-213.

[47] Bernardo, M. V., Blanco, M. D., Olmo, R., & Teijón, J. M. (2002). Delivery of bupivacaine included in poly (acrylamide-co-monomethyl itaconate) hydrogels as a function of the pH swelling medium. Journal of applied polymer science, 86(2), 327-334.

[48] Gordijo, C. R., Koulajian, K., Shuhendler, A. J., Bonifacio, L. D., Huang, H. Y., Chiang, S., ... & Wu, X. Y. (2011). Nanotechnology-enabled closed loop insulin delivery device: In vitro and in vivo evaluation of glucose-regulated insulin release for diabetes control. Advanced Functional Materials, 21(1), 73-82.

[49] Hirakura, T., Yasugi, K., Nemoto, T., Sato, M., Shimoboji, T., Aso, Y., ... & Akiyoshi, K. (2010). Hybrid hyaluronic hydrogel encapsulating nanogel as a protein nanocarrier: new system for sustained delivery of protein with a chaperone-like function. Journal of Controlled Release, 142(3), 483-489.

[50] Musch, J., Schneider, S., Lindner, P., & Richtering, W. (2008). Unperturbed volume transition of thermosensitive poly-(n-isopropylacrylamide) microgel particles embedded in a hydrogel matrix. The Journal of Physical Chemistry B, 112(20), 6309-6314.

[51] Hoare, T., Sivakumaran, D., Stefanescu, C. F., Lawlor, M. W., & Kohane, D. S. (2012). Nanogel scavengers for drugs: Local anesthetic uptake by thermostresponsive nanogels. Acta biomaterialia, 8(4), 1450-1458.

[52] Chen, P. C., Kohane, D. S., Park, Y. J., Bartlett, R. H., Langer, R., & Yang, V. C. (2004). Injectable microparticle–gel system for prolonged and localized lidocaine release. II. In vivo anesthetic effects. Journal of Biomedical Materials Research Part A: An Official Journal of The Society for Biomaterials, The Japanese Society for Biomaterials, and The Australian Society for Biomaterials and the Korean Society for Biomaterials, 70(3), 459-466.

[53] McGillicuddy, F. C., Lynch, I., Rochev, Y. A., Burke, M., Dawson, K. A., Gallagher, W. M., & Keenan, A. K. (2006). Novel “plum pudding” gels as potential drug-eluting stent coatings: Controlled release of fluvastatin. Journal of Biomedical Materials Research Part A, 79(4), 923-933.

[54] Lynch, I., de Gregorio, P., & Dawson, K. A. (2005). Simultaneous release of hydrophobic and cationic solutes from thin-film “plum-pudding” gels: a multifunctional platform for surface drug delivery?. The Journal of Physical Chemistry B, 109(13), 6257-6261.

[55] Sivakumaran, D., Mattland, D., & Hoare, T. (2011). Injectable microgel-hydrogel composites for prolonged small-molecule drug delivery. Biomacromolecules, 12(11), 4112-4120.

[56] Yeo, Y., Ito, T., Bellas, E., Highley, C. B., Marini, R., & Kohane, D. S. (2007). In situ cross-linkable hyaluronic hydrogels containing polymeric nanoparticles for preventing posturgical adhesions. Annals of surgery, 245(5), 819.

[57] Panayiotou, M., Pöhner, C., Vandevyver, C., Wandrey, C., Hilbrig, F., & Freitag, R. (2007). Synthesis and characterisation of thermo-responsive poly (N, N’-diethylacrylamide) microgels. Reactive and Functional Polymers, 67(9), 807-819.

[58] Lynch, I., & Dawson, K. A. (2004). Release of model compounds from “plum-pudding”-type gels composed of microgel particles randomly dispersed in a gel matrix. The Journal of Physical Chemistry B, 108(30), 10893-10898.

[59] Meid, J., Friedrich, T., Tieke, B., Lindner, P., & Richtering, W. (2011). Composite hydrogels with temperature sensitive heterogeneities: influence of gel matrix on the volume phase transition of embedded poly-(N-isopropylacrylamide) microgels. Physical Chemistry Chemical Physics, 13(8), 3039-3047.

[60] Lynch, I., & Dawson, K. A. (2003). Synthesis and characterization of an extremely versatile structural motif called the “Plum-Pudding” gel. The Journal of Physical Chemistry B, 107(36), 9629-9637.

[61] Galeaev, I. Y., Dainiak, M. B., Plieva, F., & Mattiasson, B. (2007). Effect of matrix elasticity on affinity binding and release of bioparticles. Elution of bound cells by temperature-induced shrinkage of the smart macroporous hydrogel. Langmuir, 23(1), 35-40.

[62] Xia, L. W., Ju, X. J., Liu, J. J., Xie, R., & Chu, L. Y. (2010). Responsive hydrogels with poly
(N-isopropylacrylamide-co-acrylic acid) colloidal spheres as building blocks. *Journal of colloid and interface science*, 349(1), 106-113.

[63] Nigro, V., Angelini, R., Bertoldo, M., Bruni, F., Castelvetro, V., Ricci, M. A., ... & Ruzicka, B. (2015). Local structure of temperature and pH-sensitive colloidal microgels. *The Journal of chemical physics, 143*(11), 114904.

[64] Hayati, M., Bardajee, G. R., Ramezani, M., Hosseini, S. S., & Mizani, F. (2019). Temperature/pH/magnetic triple sensitive nanogel-hydrogel nanocomposite for release of anticancer drug. *Polymer International*.

[65] Bardajee, G. R., Hosseini, S. S., & Ghavami, S. (2018). Embedded of Nanogel into Multi-responsive Hydrogel Nanocomposite for Anticancer Drug Delivery. *Journal of Inorganic and Organometallic Polymers and Materials*, 28(6), 2196-2205.

[66] Sivakumaran, D., Maitland, D., Oszustowicz, T., & Hoare, T. (2013). Tuning drug release from smart microgel–hydrogel composites via cross-linking. *Journal of colloid and interface science*, 392, 422-430.

[67] Sivakumaran, D., Maitland, D., & Hoare, T. (2011). Injectable microgel-hydrogel composites for prolonged small-molecule drug delivery. *Biomacromolecules*, 12(11), 4112-4120.

[68] Kleinien, J., & Richtering, W. (2011). Rearrangements in and release from responsive microgels: polyelectrolyte complexes induced by temperature and time. *The Journal of Physical Chemistry B*, 115(14), 3804-3810.

[69] Kleinien, J., Klee, A., & Richtering, W. (2010). Influence of architecture on the interaction of negatively charged multisensitive poly (N-isopropylacrylamide)-co-methacrylic acid microgels with oppositely charged polyelectrolyte: absorption vs adsorption. *Langmuir*, 26(13), 11258-11265.

[70] Lehmann, S., Seiffert, S., & Richtering, W. (2012). Spatially resolved tracer diffusion in complex responsive hydrogels. *Journal of the American Chemical Society*, 134(38), 15963-15969.

[71] Karnoosh-Yamchi, J., Mobasseri, M., Akbarzadeh, A., Davaran, S., Ostad-Rahimi, A. R., Hamishehkar, H., & Rahmati-Yamchi, M. (2014). Preparation of pH sensitive insulin-loaded Nano hydrogels and evaluation of insulin releasing in different pH conditions. *Molecular biology reports*, 41(10), 6705-6712.

[72] Rao, K. M., Rao, K. K., Ramanjaneyulu, G., & Ha, C. S. (2015). Curcumin encapsulated pH sensitive gelatin based interpenetrating polymeric network nanogels for anti-cancer drug delivery. *International journal of pharmaceutics*, 478(2), 788-795.

[73] Xiong, W., Wang, W., Wang, Y., Zhao, Y., Chen, H., Xu, H., & Yang, X. (2011). Dual temperature/pH-sensitive drug delivery of poly (N-isopropylacrylamide-co-acrylic acid) nanogels conjugated with doxorubicin for potential application in tumor hyperthermia therapy. *Colloids and Surfaces B: Biointerfaces*, 84(2), 447-453.

[74] Peng, J., Qi, T., Liao, J., Chu, B., Yang, Q., Li, W., & Qian, Z. (2013). Controlled release of cisplatin from pH-thermal dual responsive nanogels. *Biomaterials*, 34(34), 8726-8740.

[75] Rao, K. M., Mallikarjuna, B., Rao, K. K., Siraj, S., Rao, K. C., & Subha, M. C. S. (2013). Novel thermo/pH sensitive nanogels composed from poly (N-vinylcaprolactam) for controlled release of an anticancer drug. *Colloids and Surfaces B: Biointerfaces*, 102, 891-897.

[76] Demirel, G. B., & von Klitzing, R. (2013). A new multiresponsive drug delivery system using smart nanogels. *ChemPhysChem*, 14(12), 2833-2840.

[77] Bardajee, G. R., Hooshyar, Z., Farsi, M., Mobini, A., & Sang, G. (2017). Synthesis of a novel thermo/pH sensitive nanogel based on salep modified graphene oxide for drug release. *Materials Science and Engineering: C*, 72, 558-565.

[78] Zhou, N., Cao, X., Du, X., Wang, H., Wang, M., Liu, S., & Xu, B. (2017). Hyper-Crosslinkers Lead to Temperature-and pH-Responsive Polymeric Nanogels with Unusual Volume Change. *Angewandte Chemie*, 129(10), 2667-2671.

**How to cite this manuscript:** Ghasem Rezanejade Bardajee, Somayeh Ghavami, Samaneh Sadat Hosseini, A Review on pH and Temperature Responsive Gels in Drug Delivery, *Journal of Chemical Reviews*, 2020, 2(2), 80-89.