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Stimulus-Responsive Polymeric Nanogels as Smart Drug Delivery Systems

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Abstract

Nanogels are three-dimensional nanoscale networks formed by physically or chemically cross-linking polymers. Nanogels have been explored as drug delivery systems due to their advantageous properties, such as biocompatibility, high stability, tunable particle size, drug loading capacity, and possible modification of the surface for active targeting by attaching ligands that recognize cognate receptors on the target cells or tissues. Nanogels can be designed to be stimulus responsive, and react to internal or external stimuli such as pH, temperature, light, redox, thus resulting in the controlled release of loaded drug. This “smart” targeting ability prevents drug accumulation in non-target tissues and minimizes the side effects of the drug. This review aims to provide an introduction to nanogels, their preparation methods, and to discuss the design of various stimulus-responsive nanogels that are able to provide controlled drug release in response to particular stimuli.

Keywords

Nanogels; Stimulus-responsive; Drug delivery; Smart drug release; Cancer treatment

1. Introduction

In the last decade there has been considerable work carried out on stimulus-responsive nanogels, which have come to make a significant impact in the development of drug delivery systems. Nanogels have been explored by investigators as targeted nanocarriers for controlled release and improved stability of drugs in the field of nanomedicine [1,2]. Polymer nanogels used as nanocarriers in drug delivery, are materials with viscoelastic properties and with hydrophilic polymeric networks within the sub-micron size range. They can be formed by covalent bonds between polymer chains, or by non-covalent interactions, and they tend to absorb water when exposed to an aqueous medium. The internal structure of most nanogels is similar to that of hydrogels and polyelectrolyte microgels, which are only different in size and type of reaction required to produce them [3–7]. Nanogels have some unique features such as biocompatibility, high stability, adjustable particle size, and the ability to respond to external stimuli such as temperature, light, pH, ionic strength, etc. They are suitable for use in the field of tissue engineering, biomedical implants, gene therapy and drug delivery [8–10].

The hydrophilic nature of the nanogels is due to the presence of numerous polar groups such as −OH, −COOH, $-CONH_2$ and $-SO_3H$ distributed along the polymer chain [4]. The properties of viscoplastic nanogels depend on the type and concentration of the polymer building blocks used to produce them. Their overall structure is also affected by the degree of cross-linking between the monomer chains, which is adjustable with the amount and type of cross-linking agents used to produce them [11–13]. It can be said that nanogels are

formed from raw materials derived either from natural macromolecules, or from laboratory-synthesized polymers, or from a combination thereof. The natural polymeric macromolecules that exist in nature, include chitosan, dextran, and sodium alginate, and the synthetic polymers include poly (N-isopropylacrylamide), cholesterol-bearing pullulans, poly(ethylene oxide), poly(ethyleneimine) etc [14,3,5]. It is considered that most nanogels prepared from synthetic polymers carry a risk of the presence of toxic compounds within their structure, therefore various regulatory bodies have banned their use as nanocarriers in the human body.

The cross-linking process is accomplished in three locations of the nanogels themselves, including the center of the micelles, the surface, and the area between the surface and the center. Cross-linking can be accomplished by physical or by chemical methods. There are various intermolecular forces involved in the physical cross-linking of the nanogels, which include hydrophobic interactions, hydrogen bond formation, electrostatic interactions, and guest-host interactions [15,16]. In one example of this category, Shujun et al. produced nanogels consisting of water-soluble chitosan-poly(L-aspartic acid)-polyethylene glycol polymer under mild conditions, using a self-assembly mechanism based on electrostatic interactions [17].

Creation of cross-linking through chemical reactions is based on covalent bond formation, The links are based on disulfide bonds, amine reactive groups, click chemistry, or light-triggered cross-linking [18,19].

Hydrogels and nano-hydrogels can also be classified according to their type of architecture and components, which include the cross-linker structure and environmental-responsive materials. The term environmental-responsive materials or" intelligent/smart materials" refers to polymeric materials that respond to changes in the environment with a corresponding change in the polymer structure. Environmental stimuli include temperature changes, pH, light, reducing reactions and intracellular enzymes. The release of the drug from smart nanogels inside the tissue, or inside the target cell occurs rapidly. Also, whatever the drug is inside the nanogels, the response after the external stimulus is more pronounced [20].

Recently, various excellent reviews on the use of stimulus-responsive nanogels have been published in the medical area [20–23]. While some articles cover a diversity of different stimuli used for the release of a therapeutic moiety, some of them provide a more extensive discussion on a single specific type of stimulus such as pH-responsive, thermo-responsive, photo-responsive, or redox-responsive nanogels. Here we provide a more comprehensive review of stimulus-responsive nanogels, including the mechanisms of drug release, design strategies, the type of carrier materials, and their corresponding biomedical applications such as therapy for infections, inflammatory diseases and cancer, emphasizing common challenges and recent progress in the field.

2. Synthesis of nanogels

Nanogels that have been studied in the field of drug delivery are generally formed by two methods. Firstly physical self-assembly of interactive polymers, and secondly polymerization of polymers in a heterogeneous environment. The nanogel properties can be adjusted by changing the synthesis parameters such as the reaction medium, reaction time, reaction temperature, monomer type, type of cross-linking agent, the monomer ratio to the cross-linking agent concentration, and the initiator amount [24]. Polymerization techniques include precipitation [25], inverse (mini)-emulsion [26], inverse micro-emulsion [27], and dispersion polymerization [28] utilizing an uncontrolled free radical polymerization process. According to the application and synthesis method of the nanogels, the classification of their structure is summarized in Table 1.

2.1. Physical self-assembly of interactive polymers

Nanogels are formed using self-assembly of amphiphilic polymers containing active groups in their structure that produce micelles in an aqueous medium, and finally form non-covalent interactions between the chains [16,29]. One of the most important applications of self-assembled nanogels is the ability to encapsulate different protein and peptide molecules inside the polymer matrix via the formation of hydrophobic interactions [30–32]. Sawada et al. prepared a cholesterol-bearing xyloglucan (CHXG) nanogel by the hydrophobic self-assembly of a nanocarrier for trapping hydrophobic drugs, which was equipped with a galactose moiety to recognize receptors on the cell surface (Fig. 1) [33]. Jamard et al. investigated different degrees of grafting in nanogels based on hydrophobic interaction self-assembly of chains of poly(N-tert-butylacrylamide) (PNtBAm) on methylcellulose, to produce an eye-drop formulation for drug delivery. The release profile of the entrapped cargo from the nanogels could be adjusted by varying the degree of grafting and hydrophobic modification [34]. Different nanogels have been developed to take advantage of novel physical cross-linking methods. For example, cholesterol-modified poly-l-lysine which forms intermolecular double helices acting as cross-linking points, leading to the formation of an enzyme-responsive polypeptide nanogel for siRNA delivery (Fig. 2) [35]. Numerous reports on physical self-assembly of nanogels in the field of drug delivery have also been published [36–39].

2.2. Polymerization of polymers in a heterogeneous environment

One of the problems with self-assembled nanogels, is their tendency towards instability during blood circulation, but covalent polymerization produces nanogels with greater biological stability and also with more variety. There are two methods for preparing nanogels using heterogeneous polymerization, which are reverse (water/oil) and normal (oil/water) emulsions [15,49,50,26]. Many studies have been done on the preparation of hydrogels with micro- and nano-particle sizes by emulsion polymerization. The main ingredients in a typical emulsion-based polymerization reaction are oil, water, polymerization initiators, monomer solution, and surfactant as a stabilizer. The particle size can be controlled by varying their concentration, and also chemical cross-linking agents mentioned above are used [51,52]. However, one of the disadvantages this method is the need to eliminate the surfactant agent and the unreacted monomers at the end of the reaction

[53]. Hydroxyl (OH)-functionalized biodegradable nanogels that were crosslinked via disulfide bonds were synthesized for targeted drug delivery by an inverse miniemulsion. ATRP of OEOMA in the presence of DMA. The average particle size was 236±29 nm indicating an average increase in the size of the OH nanogels by 10 nm after the addition of HEA (Fig. 3) [7].

3. Targeting with nanogels

Depending on the type of active substance and the design of the nanogels, different strategies have been investigated to facilitate loading drugs into the nanogels. These are shown in (Scheme 1) (A) Permeation of drug into the nanogel, in which nanogels are added to a solution of the drug after preparation. The drug permeates into the nanogel according to the osmotic pressure and the concentration gradient, as well as via drug-polymer interactions [54]. (B) entrapment of the drug within the nanogel. In this case, a solution of the drugs and the polymer precursors is prepared, so that the drug is trapped spontaneously during the formation of the nanogel [55]. (C) Covalent bond formation, in which the drug is attached to the nanogel with chemical bonds [56,57].

The release of drugs from the nanogels depends on many factors, such as the type of drug, its interaction with the nanogel, the nanogel structure, and the environmental conditions. Therefore, the drug may be released during degradation of the nanogel, by permeation, via ion displacement, and in response to environmental stimuli, such as the temperature of the surroundings. The release of the drug occurs along with the cleavage of the bonds between the drug and the nanogel (if the drug is attached to the nanogel via chemical bonds), or via the degradation of the polymer matrix (if the drug is trapped between polymer chains) [59]. The degradation-mediated release of a model imaging reagent (monodisperse Fe_3O_4 nanoparticles) together with a model drug (fluorescently-labeled dextran) from polycarboxybetaine methacrylate nanogels formed with a disulfide cross-linker, occurred in a reducing environment. This nanogel afforded enhanced MRI performance due to R2 relaxivity, as well as the ability to be excreted by renal clearance of the disassembled nanogels (Fig. 4) [60].

Also, drug release can be carried out in the presence of environmental stimuli such as temperature and pH by changing the swelling rate. For instance in Fig. 5, DOX release occurs in a thermo-responsive nanogel. By increasing the temperature of the nanogel (T > LCST), it collapses and the drug permeates through the polymeric shell [61].

4. Recent advances in nanogels for drug delivery

In recent decades, the use of nanocarriers in the field of drug delivery has become established as a three-cornered collaboration between material science, medicine and biology. Nanogels have been shown to possess advantages, such as a small size for easier intracellular permeation, as well as a network structure, which has been shown to be stable during blood circulation, and moreover to show good biocompatibility [59]. New techniques have been used for the preparation of nanogels with controlled molecular weight values and low polydispersity. These techniques involve bioconjugation, and a controlled radical

polymerization (CRP) synthesis of copolymers [62]. Matyjaszewski at el. [63] prepared biodegradable crosslinked nanogels of well-controlled using ATRP in an inverse mini-emulsion. The nanogels prepared by ATRP, compared to the free radical polymerization nanogels, showed better-controlled degradation, higher colloidal stability, and a higher degree of swelling. The biggest advantage of nanogels in drug delivery is overcoming many biological problems, such as toxicity, low solubility, instability or inefficient transfer through biological barriers [64]. Nanogels can encapsulate various kinds of bioactive compounds such as hydrophilic and lipophilic drugs, DNA sequences, siRNA, peptides and proteins inside their network [65,66,67]. Shimizu et al. [68] investigated the encapsulation of proteins inside nanogels composed of amphiphilic cholesterol modified pullulan assembled by non-covalent interactions. One of the important advantages of nanogels in drug delivery is the ability to optimize their structure to overcome extracellular barriers that reduces their therapeutic efficacy. Therefore, by modifying the surface of the nanogels with hydrophilic polymers and ligands, improvements in performance have been achieved (Fig. 6). Imparting a hydrophilic surface to the nanogel can: (a) increase their circulation time in the bloodstream; (b) reduce their phagocytosis by immune cells; and (c) inhibit particle uptake by the mononuclear phagocytic system by reducing non-specific interaction with serum proteins (opsonization) [69–71]. Many researchers have modified the surface of the nanogels with receptor-specific ligands such as an antibody or an aptamer for active targeting to specific cell types. Chiang et al. [72] developed a DOX-loaded pH/thermodual responsive nanogel composed of poly(N-isopropylacrylamide) (PNIPAAm)-block-monomethoxy poly(ethylene glycol) with a hydrophilic PEG corona and acrylic acid (AAc)-co-2-methacryloyloxyethyl acrylate (MEA) that functioned to protect the nanogels and prolong the retention time in cancers. Wang et al.[73] designed a DOX-loaded nanogel composed of poly (N-isopropyl acrylamide-co-acrylic acid) and modified with RGD peptides to increase both the vascular and tissue permeability in a tumor-specific manner.

5. Toxicity of the nanogels

The toxicity of nanogels used in drug delivery is a very important issue. Acrylate and methacrylate-based polymer nanogels are not yet used routinely in the field of medicine due to the presence of potentially hazardous components in their chemical structure [75]. Also, the continued presence of unreacted monomers, surfactants, oligomers and initiators left behind after the preparation of nanogels is another issue in the field. To solve these problems, purification measures have been investigated, including extensive washing of the final product and changes to modify the polymerization kinetics. The use of gamma radiation and physical self-assembly techniques can be used for preparing nanogels, without the use of polymerization initiators and cross-linking agents, which might to reduce the toxicity [76,32]. The extract dilution, direct contact, and agar diffusion tests together with cell culture methods have been widely used to evaluate the toxicity of hydrogels or nanogels. Other non-toxic nanogel systems have been synthesized using biocompatible natural polymers such as alginate, dextran, pullulan and hyaluronic acid. Studies have shown that the cells exposed to these nanogels have a high survival rate, which is evidence of low toxicity [77–80].

6. Stimulus-responsive nanogels

6.1. pH-responsive nanogels

Many studies have been reported on pH-sensitive materials in the field of medicine in order to reduce drug toxicity in the body and achieve more targeted drug delivery. Because of the different pH values observed in healthy tissues (pH = 7.4), stomach (pH = 1.0 − 3.0), and tumor tissues (pH = 6.5−7.0), nanogels have been designed to be sensitive to the particular pH range of interest allowing drug release only in the tissue to be targeted [81–84].

Nanogels can show swelling behavior or collapsing behavior caused by protonation or deprotonation of anionic or cationic groups contained within the network. Anionic nanogels include carboxylic acid or sulfonic acid groups. If the pK_a of the polymer is larger than the pH of the environment, the ionic structure leads to increased electrostatic repulsion within the network leading to overall swelling. On the other hand, cationic nanogels possess terminal amino groups, so that if the pH of the environment around the gel is less than that of the pK_b,, the amino groups change from NH_2 to NH_3^+, thus increasing the hydrophilic character, the electrostatic repulsion and the swelling rate. This can also be said to involve a change in the hydrophobic/hydrophilic phase transition [85–88]. Nanogels tend to be more physically stable in physiological environments compared to other nanocarriers. Nanogels containing poly(l-Asp) used in drug delivery systems cause the breakdown of the lysosomal membrane, which then leads to release of many kinds of hydrolysis enzymes such as phosphatases, proteases, and nucleases which can kill the neighboring host cells [89,90]. One study used DEAP groups that have a pK_b~6.8 within the poly(l-Asp) blocks acting as the core of the nanogel. The DEAP groups are protonated below pH 7.0 leading to swelling of the nanogels. The surface was initially stabilized through ring polymerization, while chemical cross-linking using disulfide bonds sustained it during blood circulation. Different amounts of poly(d, l-lactide-co-glycolide) were used for the volume change of pH-responsive nanogels in more acidic environments. The results showed that by increasing the amount of the poly(d, l-lactide-co-glycolide) in the nanogel, the particle size increased when the pH reduced from 7.0 to 5.0 the transmittance reduced showing drug release (Fig. 7).

Figure 8 shows that the tumor-targeting of nanogels was successfully carried out by neutralization of the lysosomal pH using nanogels with lysosomotropic amines [91]. Many similar studies also report the construction of pH-responsive nanogels. For example, William et al. [84] used cationic polymers formed from 2-(diethylaminoethyl) methacrylate (DEAEMA) prepared with poly(ethylene glycol) methyl ether methacrylate copolymer. The effects of TBMA and TBAEMA on the aqueous solution properties of poly(ethylene glycol)methyl ether methacrylate (PEGMA)-grafted DEAEMA nanogels were investigated. PDMAEMA polymers in the protonated state undergo electrostatic interactions with DNA and proteins due to the amine side groups that have a pKa of 7.7−8.1 [92,93]. The results showed that P(DEAEMA-co-TBMA-g-PEGMA) nanogels with an increasing TBMA content, reached a maximum swelling volume at pH 5.50, but in P(DEAEMA-co-TBAEMA-g-PEGMA) nanogels (due to the presence of several species of ionized groups) many changes were not observed. Therefore, they suggested that P(DEAEMA-co-TBMA-g-PEGMA) nanogels should be more efficient for smart intracellular drug delivery.

Nevertheless, nanogels are still not used in clinical applications, due to limitations such as:

1. short circulation time
2. low drug loading and poor uptake
3. poor stability before reaching the target
4. biodegradability after reaching the target

Many methods and strategies have been developed to overcome these limitations, such as: (a) the use of biodegradable cross-linkers after complete release of the drug; (b) the use of conjugation-based polymers; (c) the use of hollow nanogels to increase drug loading; (d) the use of antifouling materials such as PEG that increase stability and prolong blood circulation time [94,96,97]. Hajebi at el. designed hybrid, hollow nanogels based on PDMAEMA polymers **prepared**by inverse emulsion polymerization using different amounts of chemical cross-linking agents, comparing the loading of the drug DOX and its release rate in pH-responsive nanogels. They demonstrated that the drug loading rate in hollow nanogels with a low density was higher in biologically relevant conditions, than the hybrid hollow nanogels with a higher density, but the release rate of the hybrid nanogel was higher than the hollow nanogels in a collapsed state. In another study, Ruairí at el. [98] reported a high loading capacity of poly((2-dimethylamino)ethyl methacrylate) (PDMAEMA) nanogels as pH-sensitive carriers with increased mucoadhesive properties for ocular drug delivery by quaternization of the amino groups (Fig. 9).

Due to the relatively inefficient targeting ability of some nanogels that rely solely on the EPR effect, active targeting has been explored to improve tumor-targeting ability. These targeting ligands have included peptides, folic acid, antibodies and hyaluronic acid (HA), which have all have been used for targeted cancer therapy. For example, Yang and colleagues investigated the penetration and antitumor efficacy of pH-triggered hyaluronic acid-functionalized nanogels prepared by cross-linking with ortho-ester groups that undergo degradation in acidic media (Fig. 10). They first synthesized the ortho-ester cross-linker by aqueous dispersion polymerization of a nanogel of methacrylic anhydride. The nanogel was loaded with the therapeutic drug DOX and tagged with hyaluronic acid. The results showed that the drug release was minimal at neutral pH, and increased under the acidic conditions of the tumor [99].

6.2. Temperature-responsive nanogels

Temperature is a stimulus, which can be used for smart drug delivery to tumors and areas of inflammation that typically display elevated temperatures ranging from 40 – 45 °C [100,101]. Temperature-sensitive nanogels are stable during circulation, but show much faster release kinetics as compared to hydrogels. Temperature-dependent polymeric nanogels exhibit either swelling or shrinkage in response to temperature variation (Fig. 11).

Temperature-sensitive nanogels show a response to a temperature above normal physiological temperature. For instance, poly(N-isopropylacrylamide-co-acrylic acid) (PNIPAM) undergoes a reversible lower critical solution temperature (LCST) phase transition when heated in water above 32 °C. It changes from a swollen hydrated state to a

shrunken dehydrated state, losing about 90% of its volume. Poly(vinylcaprolactam) (pVCl) has a temperature response range between 30–50 °C, while that of poly(N,N-diethylacrylamide) (PDEAAm) has been reported to be around 30–32 °C. All these polymers have been used to release their cargo to the target site where the temperature is elevated, or where external heat is applied [102].

Temperature-responsive nanogels can be divided into two groups: polymeric nanogels with a negative temperature sensitivity, and polymeric nanogels that have a positive temperature sensitivity. Negative temperature sensitivity is defined as lower critical solution temperature (LCST). In the structure of these nanogels, hydrophilic and hydrophobic groups such CONH and alkyl groups are incorporated [103]. At temperatures lower than the LCST, the polymers are in a swollen state due to hydrogen bond formation between water and the hydrophilic polymeric parts, but by increasing the temperature above the LCST, the hydrophobic interactions between the hydrophobic polymeric part dominate, and overcome the hydrogen bonds causing the network to collapse [104,105].

The positive temperature sensitivity of the polymer hydrogel is defined by a higher critical solution temperature (UCST), which leads to the collapse of the nanogels at a temperature lower than the UCST, while swelling occurs at temperatures higher than the UCST [107,108]. The epidermis and stratum corneum of the skin acts as an effective barrier to prevent penetration of topically applied drugs. Preparing nanogels by the layer-by-layer (LBL) technique, controls the chemical composition, nanoscale thickness, mechanical properties and converts a burst release mode to a sustained release mode [109,110]. Zavgorodnya et al. [111] investigated the loading behavior and release of the sodium diclofenac drug cargo in poly(N-vinylcaprolactam) (PVCL-(based temperature-sensitive core-shell nanogels, that were prepared by the layer-by-layer (LbL) hydrogen-bonded technique to control the nanoscale thickness. The results showed that the release of sodium diclofenac above the LCST of the polymer (LCST ~32°C) was higher than lower than the LCST. Moreover, by increasing the thickness of the polymeric layers the swelling behavior was reduced (Fig. 12).

Two of the most challenging issues in multi-layer nanogel systems, are the increased size of the nanoparticles, as well as the complexity of the drug release process. In one study, Deshpande and coworkers used gold nanoparticles (AuNPs) as a core with synthesized pNIPAm chains. To form core-shell nanogels, and by loading the DOX drug onto the shell, investigated the drug release behavior at different temperatures with varying compositions of pNIPAm. The characteristics of the AuNPs included bio-inertness, biocompatibility and the optical resonance of their surface plasmons. The results showed that these nanogels were stable under biological conditions, and the release of DOX could kill more cancer cells than single-system nanoparticles (Fig. 13) [112]. There is a wide range of synthetic and natural polymers that exhibit a LCST around the physiological temperature (Table 2).

6.3. Redox-responsive nanogels

Nanogels that are responsive to redox stimulation often contain cross-linking formed by disulfide bonds, and have received considerable attention due to the high concentrations of reducing agents such as thioredoxin, reduced glutathione (GSH) and peroxiredoxin inside

cells, compared to their concentration in the extracellular environment [63,117,118]. The higher glutathione concentration in cancer cells compared to healthy cells, has been extensively exploited as a therapeutic strategy to trigger controlled drug release inside the tumor [119]. Noree et al. [120] formed amphiphilic random copolymers from PPFPMA-co-POEGMAMbpoly(pentafluorophenyl methacrylate)-co-poly(oligo(ethylene glycol methacryl amide)), by post-polymerization modification, then after self-assembly into micelles, used the addition of cystamine as a cross-linking agent to produce redox-responsive nanogels. During the formation of the micelles, they encapsulated a hydrophobic drug inside, and examined the release behavior in the presence and absence of GSH (Fig. 14a and b).

Recently, a new bio-reducible cross-linked dextrin nanogel called AMD3100 containing the ligand CXCL12 (SDF-1) that recognizes the receptor CXCR4, which is present on the surface of the cell membrane, to prevent the metastasis of breast cancer cells to the lungs and lymph nodes by targeted anticancer drug delivery (Fig. 15). H&E staining of lung tissue segments and lung lesions in Balb/C mice showed the DOX-AMD-DNG treated group had no lesions in their lungs, and the anti-metastatic effect was weaker in the non-targeted AMD3100 or free DOX groups than in the DOX-AMD-DNG group (Fig. 16) [121]. Lee et al. [122] investigated the encapsulation of a curcumin-derived chemotherapeutic agent, as a water-soluble anti-cancer drug in poly(DTPA-co-Cys) polyionic complex nanogels that were prepared by redox-responsive cross-linking. Redox-responsive nanogels can also be prepared by adding bioreducible, bifunctional monomers into the reaction mixture during post-polymerization or during emulsion [123,124].

6.4. Light-responsive nanogels

Near-infrared (NIR) light with wavelengths in the range of 650 to 900 nm has recently been considered to be a stimulus to trigger drug release, with advantages such as mild reaction conditions, high biocompatibility, ability for in-situ polymerization for specific applications, lower toxicity, less usage of organic solvents and less by-product formation. Moreover, the photoreaction can also be reversible. NIR radiation can penetrate farther than 10 cm into tissue under some circumstances [125–127]. Photo-responsive polymeric nanogels often contain acrylic or coumarin-based bonds that cleave under illumination causing drug release (Scheme 2) [128,129].

Chromophore groups attached to the polymer backbone can absorb light leading to isomerization, cleavage or dimerization in photo-responsive nanogels. In particular cross-linking density can be controlled, and the stability of the nanogels can be better adjusted by controlling the light wavelength, energy or time of irradiation. This concept can be exemplified by the vinyl groups of the acrylic groups that can be cross-linked by UV light in poly(D,L-lactic acid)/poly(ethylene glycol)/poly(D,L-lactic acid) (PLA-PEG-PLA) nanogels described by Lee et al. The swelling and the size of the nanogels decreased after their exposure to UV light, along with the increased density of cross-linking. The authors observed that the sustained release of hydrophobic drugs occurred from irradiated nanogels [64]. He and Zhao synthesized a random copolymer of 4-methyl-(7-(methacryloyl)oxy-ethyloxy) coumarin and methyl methacrylate (P(CMA-co-MMA)) as the hydrophobic block,

and poly(ethylene oxide) (PEO) as the hydrophilic block, and micelles were formed in an aqueous solution by increasing T > LCST. Subsequently, the coumarin groups underwent a cycloaddition reaction under UV irradiation (λ < 310 nm) giving rise to cross-linked nanogels [130]. Hyaluronic acid (HyA) is a natural polysaccharide formed from disaccharide units of N-acetyl-D-glucosamine and D-glucuronic acid with b(1,4) and b(1,3) glucosidic bonds, and the ability to recognize the HyA receptor known as CD44, which is a high affinity HyA receptor that is over-expressed on various cancer cells [131]. Hang and coworkers reported that UV-responsive degradable nanogels formed from hyaluronic acid-g-7-N,N-diethylamino-4-hydroxymethylcoumarin (HA-CM), allowed CD44-targeted delivery of DOX, with release triggered by NIR irradiation. The coumarin moiety has a high two-photon absorption cross-section for NIR excitation, and one-photon UV excitation both triggered drug release. The results of the in vitro studies demonstrated that DOX-loaded nanogels irradiated by UV had a higher drug release than NIR, due to the cleavage of the urethane bonds under UV irradiation. They also showed effective uptake by CD44+ MCF-7 cells via a receptor-mediated pathway, and intracellular DOX release under NIR irradiation (Fig. 17) [132].

The azo-bond moiety undergoes photo-isomerization under UV-vis light, changing from cis to trans conformation. Azo-bonds can be incorporated into a polymeric backbone, and in an aqueous medium, light changes the physical and chemical properties such as rate of swelling and morphology. For example, Patnaik et al. [127] synthesized non-covalently cross-linked azo-dextran nanogels loaded with rhodamine B and aspirin, and under UV light (365 nm) the drug release behavior of the Z-isomer in the nanogels was higher than that of the E-isomer.

6.5. Multi-stimuli responsive nanogels

More recently, researchers have prepared nanogels that are responsive to more than one type of stimulus. Multi-responsive nanogels may show improved sensitivity and specificity to target tumors, compared to single stimulus-responsive nanogels. These nanogels can release their cargos, changing their configuration, dimensions, chemical or physical properties in response to a combination of pH, temperature, redox, and light stimulus. In this section, we will discuss nanogels that respond to a combination of these various stimuli.

6.5.1. pH/Temperature dual-responsive nanogels—There are many conditions in which changes in both tissue pH and temperature are observed simultaneously. By designing dual temperature-/pH-responsive drug nanocarriers it is possible to combine the independent sensitivity of each stimulus in one nanocarrier. When only temperature-sensitive polymers are used, the targeting of cancer cells is difficult, but if the nanogel is simultaneously responsive to both temperature and pH, it can increase the selectivity for cancer cells, as shown in Fig. 18 [56].

Cancer cells can show acquired drug resistance and a heterogeneous response to chemotherapy, and combination chemotherapy is an alternative approach. Multi-responsive nanogels may be designed with multi-drug release systems to control the release behavior of each drug separately. In addition, super-paramagnetic nanoparticles (MNPs) can be excited

by an alternating magnetic field leading to hyperthermic effects, resulting in selective cancer destruction [133]. In one study, dual temperature/pH-sensitive superparamagnetic nanogels were fabricated with temperature-responsive poly(N-isopropylacrylamide) P(NIPAAm) and N,N-dimethylaminoethyl methacrylate (DMAEMA) containing amino end groups with pH-responsive behavior. The purpose was to simultaneously deliver two different anticancer drugs, doxorubicin (DOX) and methotrexate (MTX) with different response triggers. The results that when the nanogels were incubated in medium with low pH and high temperature, the hydrolysis of the hydroxyl groups led to electrostatic repulsion, and collapse of the nanogel, and both drugs released faster (Fig. 19 a and b) [134].

In another example, Chiang et al. synthesized hollow nanogel spheres, sensitive to variations in both pH and temperature as an efficient intracellular drug delivery vehicle. It was obtained from spontaneous co-association of the copolymers acrylic acid (AAc) and 2-methacryloylethyl acrylate (MEA) units, with another chain either alone or as both PNIPAAm poly(N-isopropylacrylamide) (PNIPAAm) and monomethoxypoly(ethylene glycol) (mPEG) as grafts. In acidic conditions (pH 5 at 37 °C) the AAc/DOX complexes showed reduced ionization and shrinkage of the nanogels, but at neutral pH, they showed the highest stability. The DOX-loaded hollow nanogels showed a cytotoxic effect comparable to free drug with less toxicity and the potential for anticancer treatment [135]. In another study, Jin et al. [136] demonstrated the druv-release properties of ibuprofen (IBU) from poly(N-isopropylacrylamide-co-acrylic acid) P(NIPAM-co-AA) nanogels depending on the copolymer composition, swelling characteristics and dispersion state under different conditions. Due to the electrostatic repulsion and hydrophilicity they showed high cumulative release in response to pH 7.4 (pH value higher than pK_a of AA) and a temperature of 37 °C.

6.5.2. pH/Redox dual-responsive nanogels—As previously mentioned, the concentration of GSH in tumor tissues about 4-fold higher than in normal tissues. Moreover the concentration of GSH in the cytoplasm (0.5−10 mM) is 100−1000 times higher than that in the cellular exterior (about 2−20 μM) [137]. Recently, Lian et al. prepared poly(ethylene glycol)-graft-dextran (CDP) nanogels by cross-linking with various amounts of 3,30-dithiodipropionic acid (DTPA) for dual reduction-triggered and pH-responsive drug delivery which had showed high cytotoxicity against various types of cancer cells (Scheme 3).

In the presence of GSH and at lower pH, by simultaneous cleavage of disulfide bonds and protonation of the amino groups of DOX leading to dissociation of the electronic interaction between DOX and residual carboxyl groups in the DTA cross-linker, the rate of release increased [138]. Zuo and coworkers created pH/redox dual-responsive nanogels by simple ionic gelation between negatively charged O-carboxymethyl-chitosan (CMCS) and positively charged thiolated chitosan (TCS), Then the CMCS-TCS nanogels (CTNGs) were formed via oxidation of the thiol groups to disulfide bonds. DOX/CTNGs were stepwise-responsive to their intracellular environment after endocytosis. They self-precipitated in response to endo/lysosome acidic pH, and underwent cleavage of disulfide bonds in the cytoplasm and disintegrated in the nucleus due to elevated GSH concentrations. The negatively charged surface of the nanogels led to their stability during circulation [139]. How et al. created a polyionic complex (PIC) dual reduction/pH-responsive nanogel from

lactobionolatone/lipoic acid-modified poly(L-lysine) (PLL) and poly(acrylic acid) (PAA) via disulfide bond formation between PLL. Cellular uptake showed that Lac-conjugated nanogels (containing glucose) bound to the cells bearing asialoglycoprotein receptors and delivered DOX into the HepG2 cells in a more efficient manner. Subsequently the drug was released in the acidic endosomal compartment or in the presence of GSH to cleave the disulfide bonds [140].

7. Conclusions

In recent years nanocarriers have received tremendous amounts of attention in drug delivery research. Due to their structural variety, they can be modified to package and transfer loaded cargo to the intended location. Nanogels consist of hydrophilic polymeric networks at sub-micron sizes. Nanogels are characterized by high water absorption, good biocompatibility, high stability and also offer interesting opportunities for drug loading with low toxicity. Nanogels can be synthesized using a variety of methods, and the chosen method affects the final properties of the nanogel. The amount of drug release is adjustable by changing the cross-linking agent, which is not possible in the case of micelles. Drugs can be loaded either before or after the preparation of the nanogel using either covalent bond formation or electrostatic interaction. Depending on the structure of the nanogel and the drug interaction, drugs can be released by breaking the chemical bonds or degradation of the nanogel matrix. Nanogels have the ability to encapsulate biologically active compounds such as proteins, and DNA or RNA within the nano-pockets inside the polymer network. In order to increase the efficiency of transport and to protect the drug against decomposition in biological systems, the surface of the nanogels can be modified with hydrophilic polymers. Active-targeting can be achieved by attaching ligands that recognize biological receptors expressed on the outside of target cells.

Smart internal stimulus-responsive nanogels responding to intracellular stimuli such as pH, redox, photo, and temperature, can release the drug cargo at specific locations and with controllable kinetics. The drug-carrying nanogels can undergo triggered release as a result of changes in structure caused by the stimulus (e.g. COOH, NH_2, coumarin groups) leading to swelling or collapsing. The structural instability of the carrier and bond cleavage leads to the leakage of the drug contents. It has to be stressed that the responsive stimuli should be in agreement with the desired target, and the release of the drug should not occur in the extracellular environment. The use of nanogels as a drug delivery carrier can improve the efficiency of drugs like cancer chemotherapy and can also be used for imaging reporter molecules.

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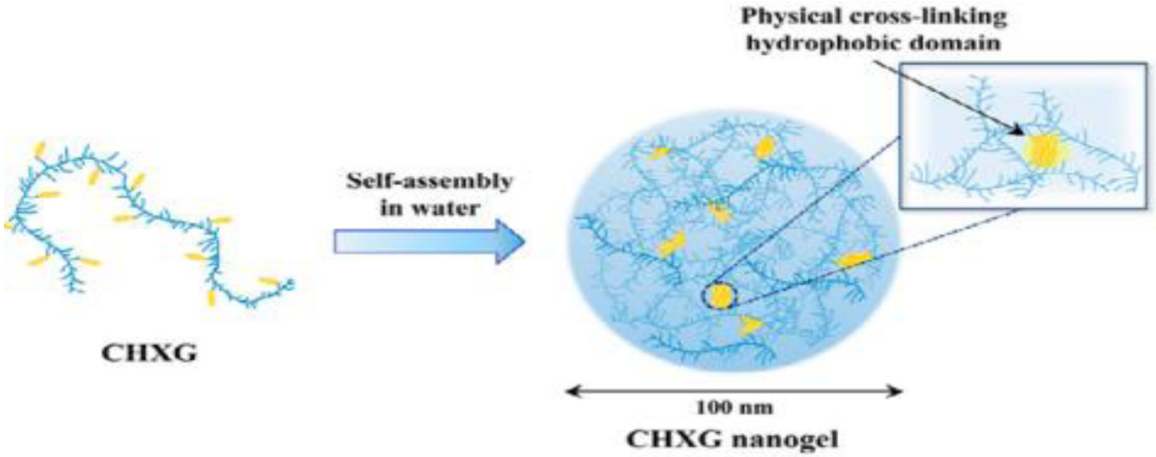


Figure 1.
Schematic representation of cholesterol-bearing xyloglucan (CHXG) nanogels [33]. Copyright Taylor and Francis, reprinted with permission

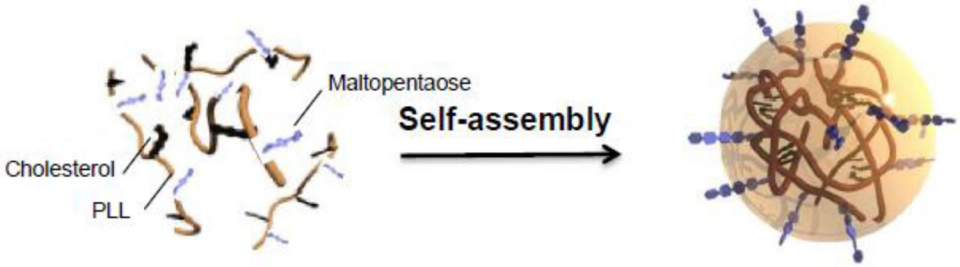


Figure 2.
Self-assembled polypeptide nanogels [35]. Copyright American Chemical Society, reprinted with permission

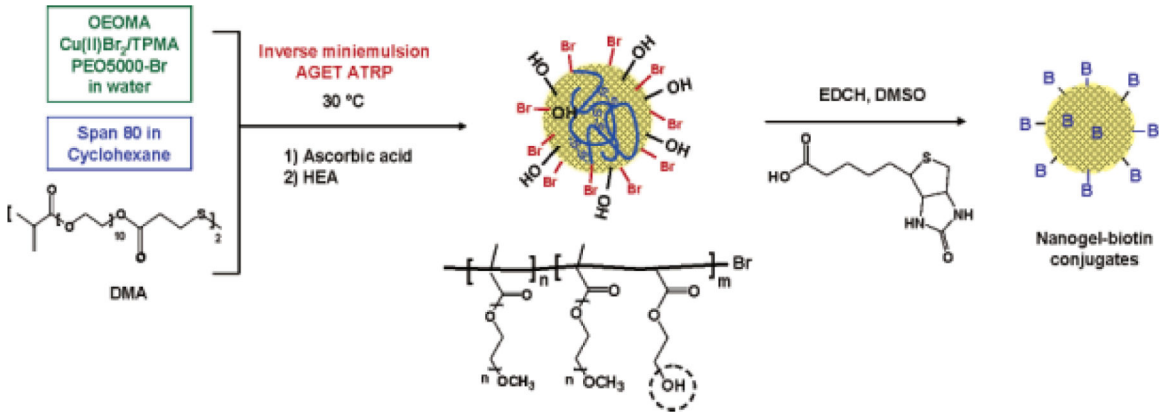


Figure 3.

OH-functionalized nanogels by ATRP in inverse miniemulsion [7] Copyright American Chemical Society, reprinted with permission

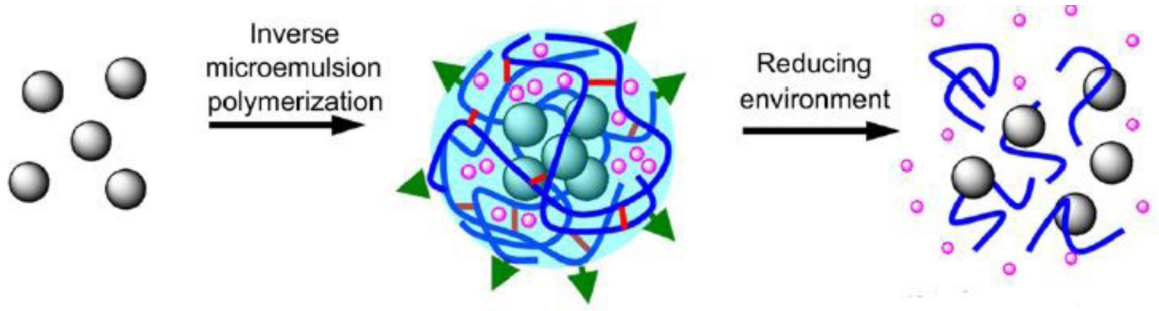


Figure 4.
Degradation of nanogel and release of drugs [60]. Copyright Elsevier, reprinted with permission

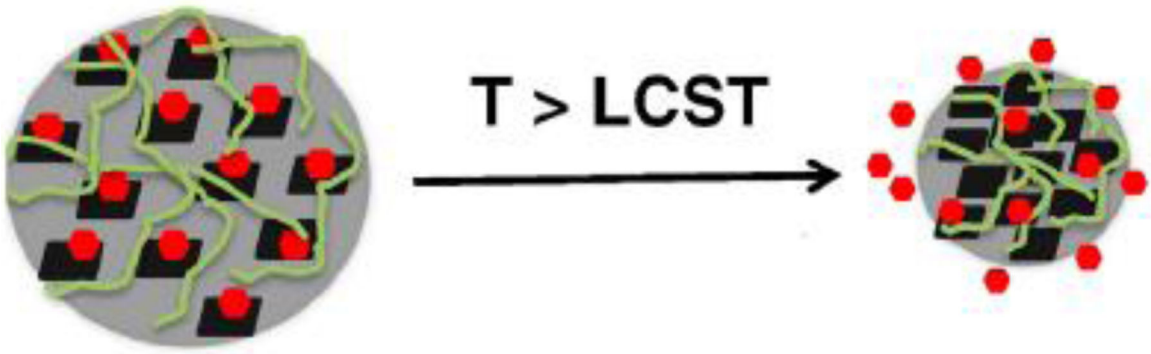


Figure 5.
Permeation release in nanogel [61] Copyright Elsevier, reprinted with permission

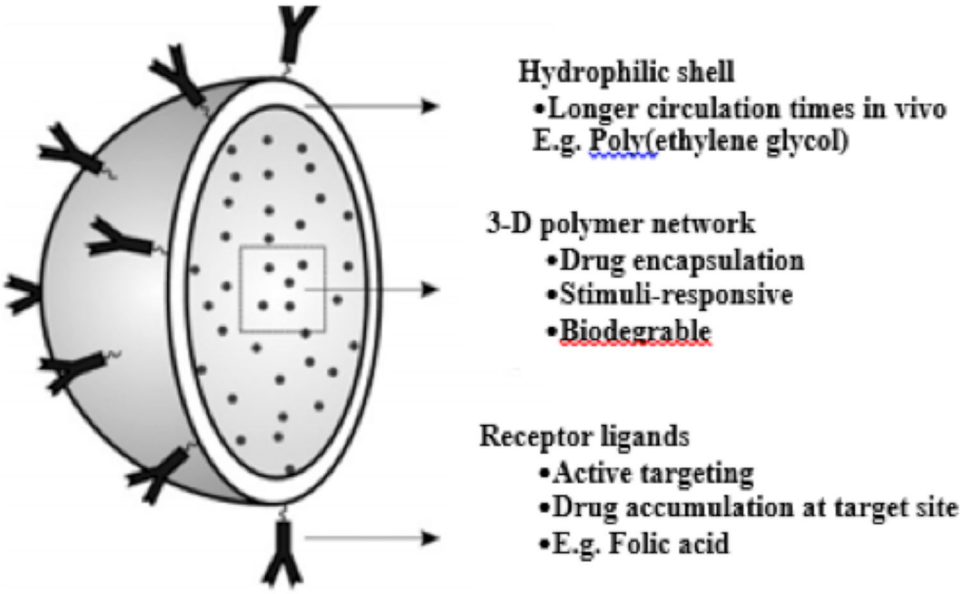


Figure 6.

multi-functional of stimuli-responsive nanogels via targeted ligands and a hydrophilic shell for clinical applications [74] Copyright Royal Society of Chemistry, reprinted with permission

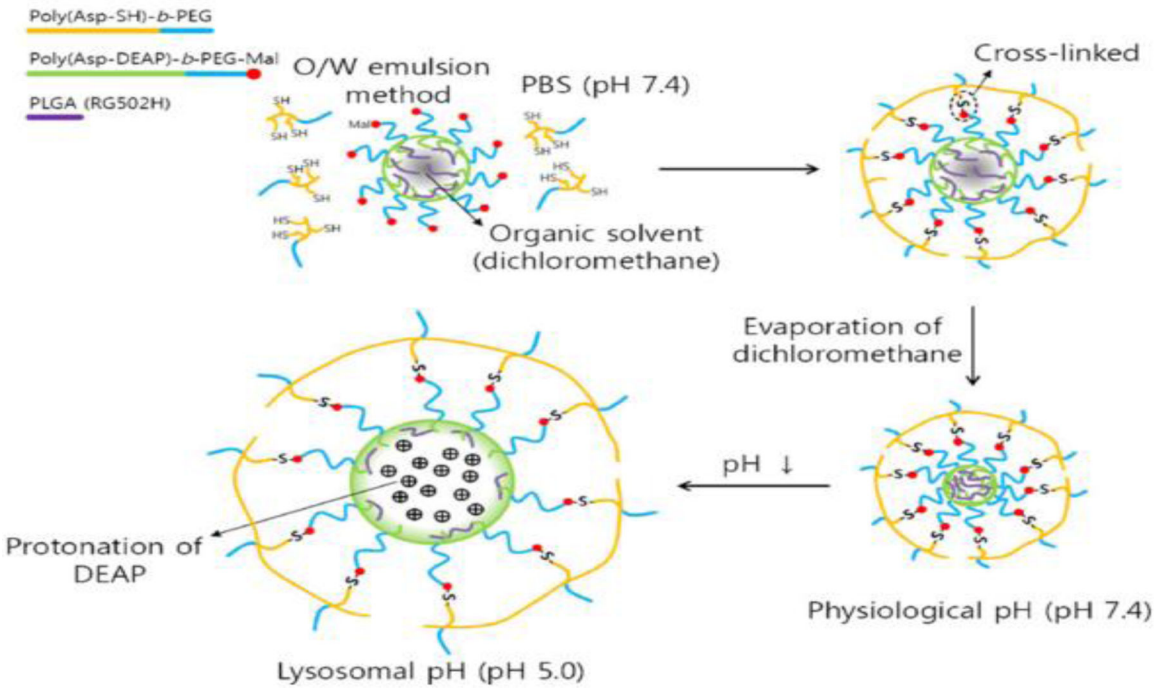


Figure 7.

The pH-responsive of poly(l-Asp) derivative nanogels in different pH [91] Copyright Elsevier, reprinted with permission

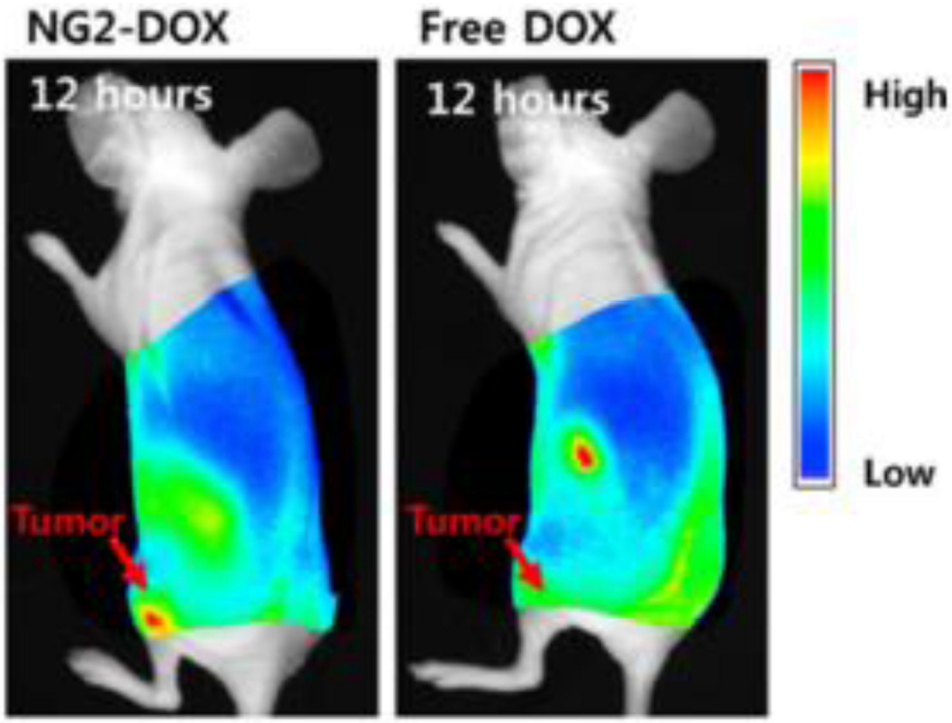


Figure 8.
Non-invasive fluorescent imaging of uptake DOX-loaded nanogels or free DOX injected into tumor-bearing nude mice [91] Copyright Elsevier, reprinted with permission

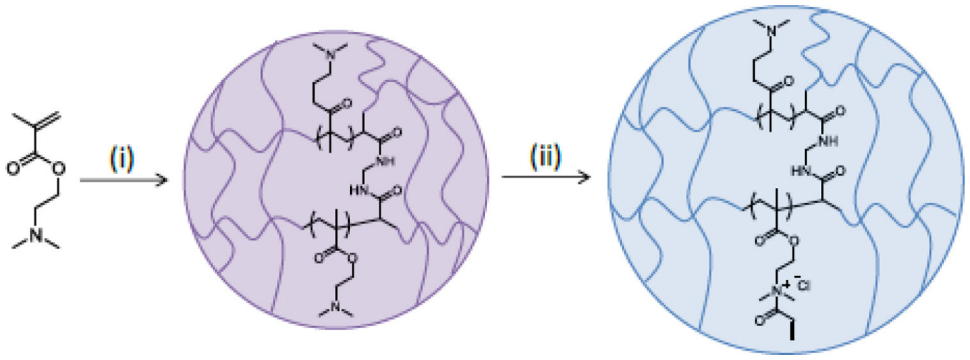


Figure 9.
Synthesis of quaternized PDMAEMA nanogels [98]. Copyright Elsevier, reprinted with permission

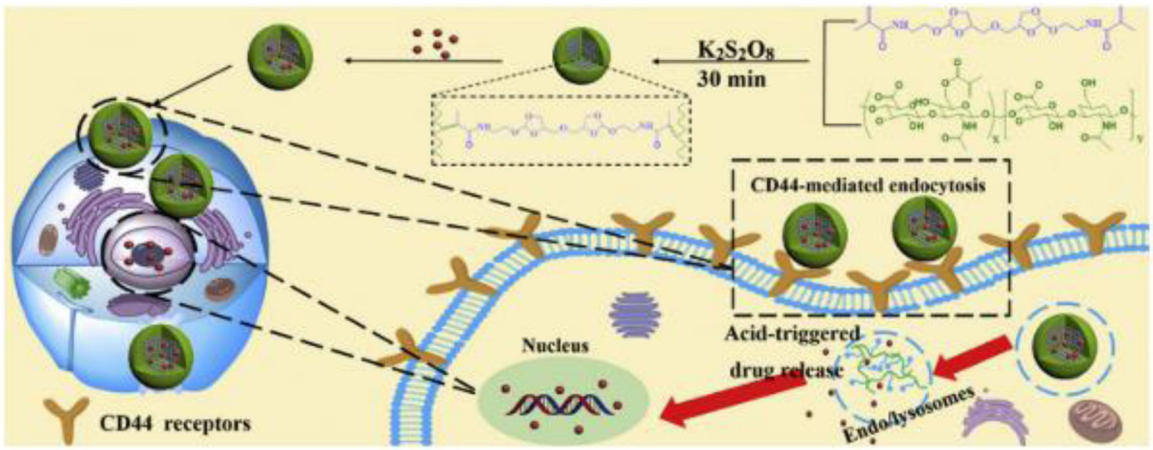


Figure 10.
Scheme of the targeted DOX release from pH-triggered HA-NGs [99] Permission required?

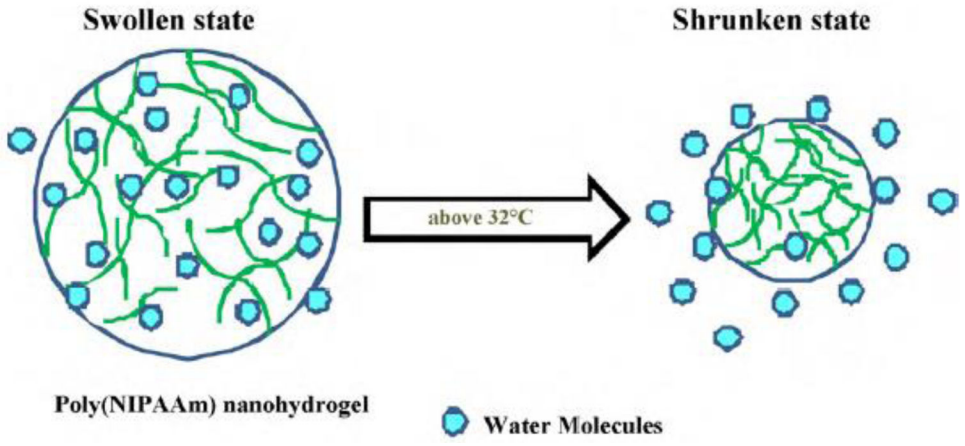


Figure 11.

T-responsive nanogel for Fe_3O_4 encapsulate and water molecules release by increasing temperature [106] Copyright Elsevier, reprinted with permission

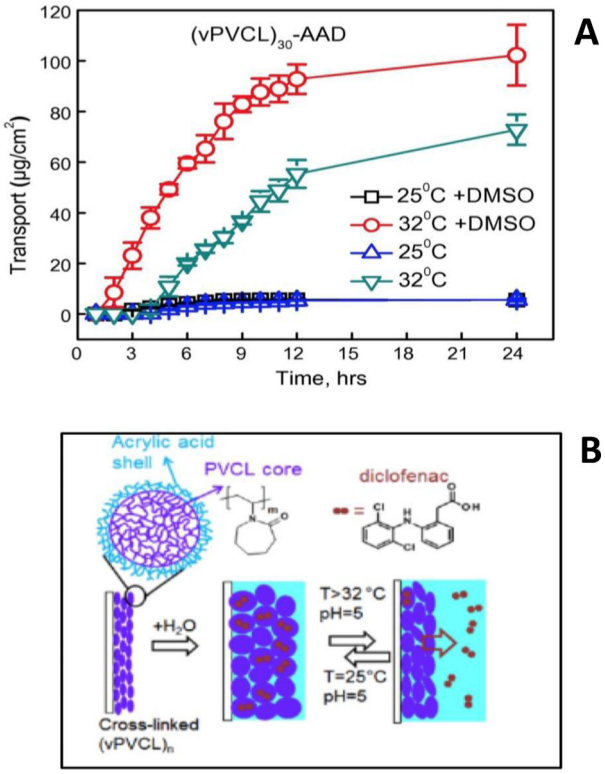


Figure12.

Transport of diclofenac from the (vPVCL) multilayer nanohydrogel at temperatures: 25 and 32 °C (a) Responsiveness of the nanohydrogel to the temperature and release of the drug [111] Copyright Elsevier, reprinted with permission

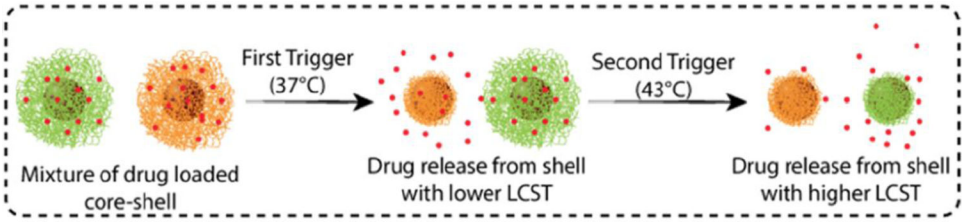


Figure 13.

Temperature-dependent release of a drug from a nanogel in varying conditions [112] Copyright Elsevier, reprinted with permission

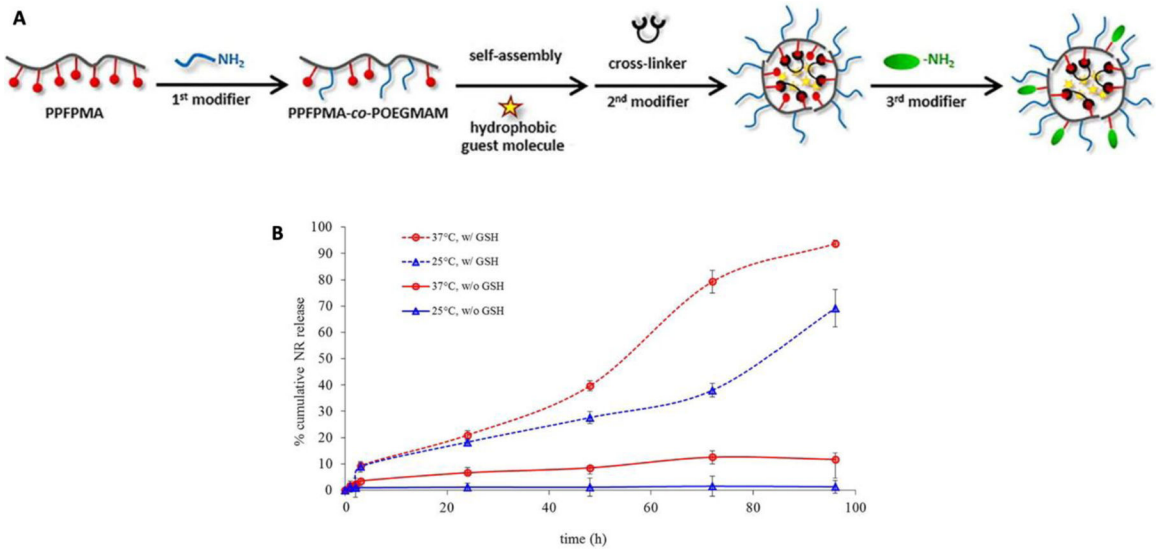


Figure 14.

post-polymerization modification of PPFPMA with amine modifiers toproduce a redox-responsive nanogels (a), release profiles from nanogels in presence and without GSH (b) [120] Copyright Elsevier, reprinted with permission

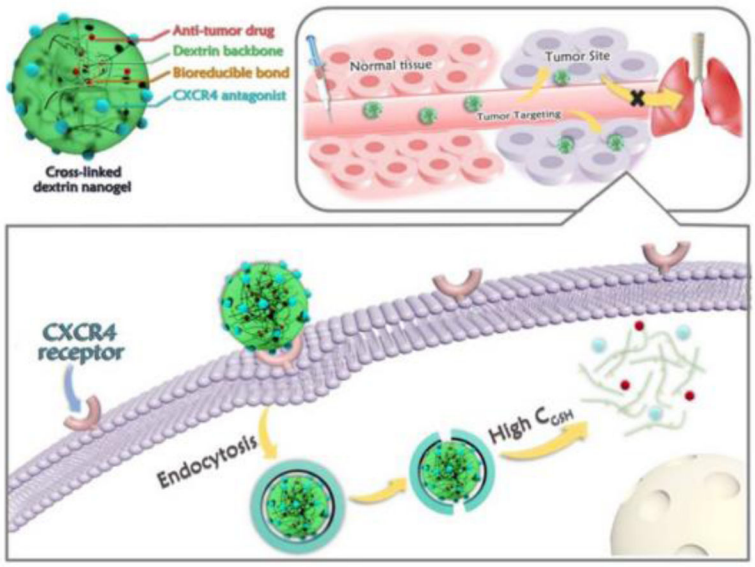


Figure 15.

Schematic illustration of controlled release by a novel CXCR4-ligand modified DOX-encapsulated dextrin nanogel at the tumor site [121] Copyright American Chemical Society, reprinted with permission

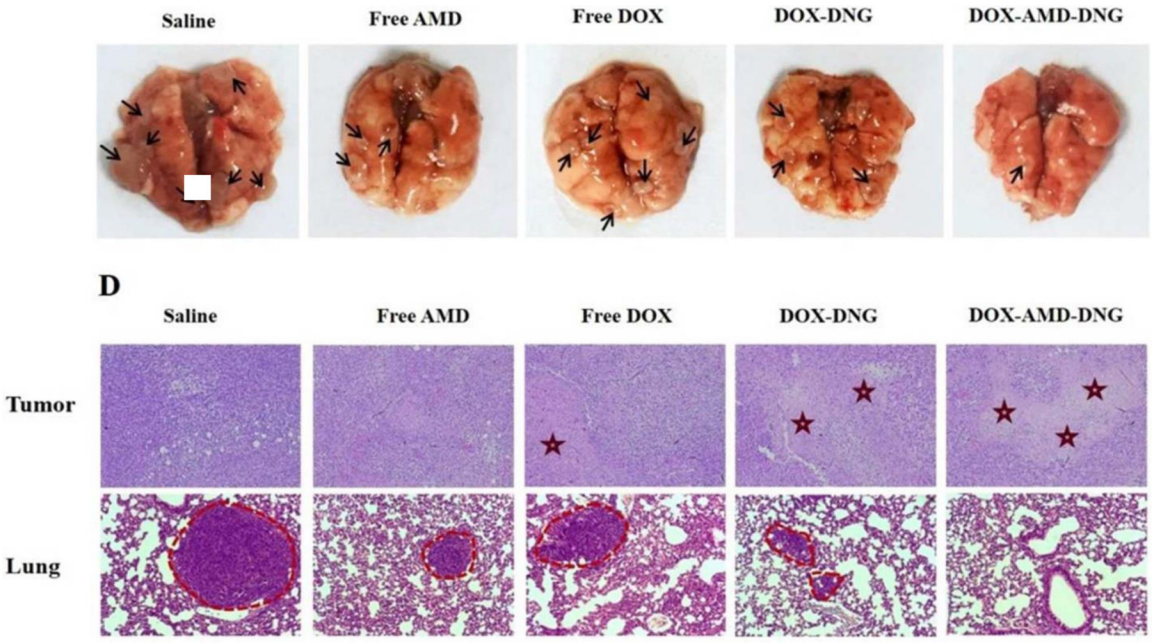


Figure 16.

Saline effects, free AMD, free DOX, DOX-DNG and DOX-AMD-DNG on mouse lung [121] Copyright American Chemical Society, reprinted with permission

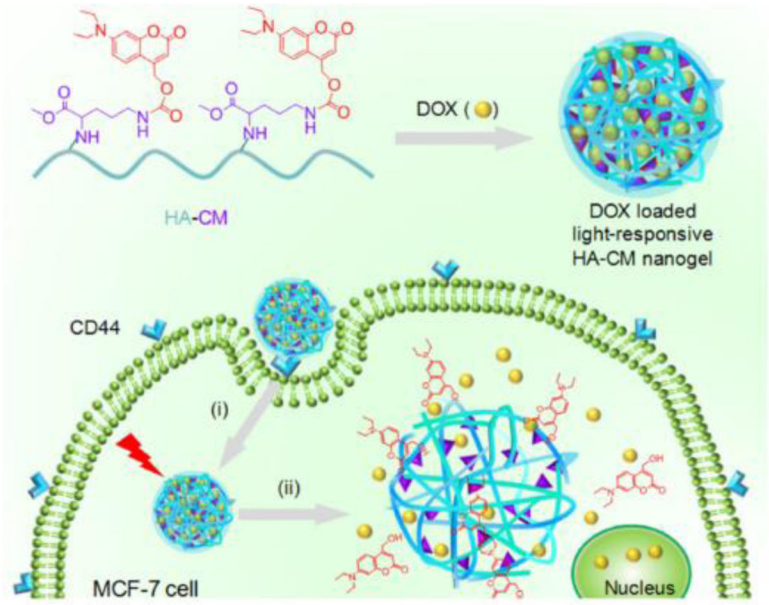


Figure17.

Light-responsive HA-CM nanogels for CD44 targeted and remotely controlled DOX delivery. (i) Receptor-mediated endocytosis, and (ii) nanogel swelling and drug release upon light irradiation [132] Copyright Elsevier, reprinted with permission

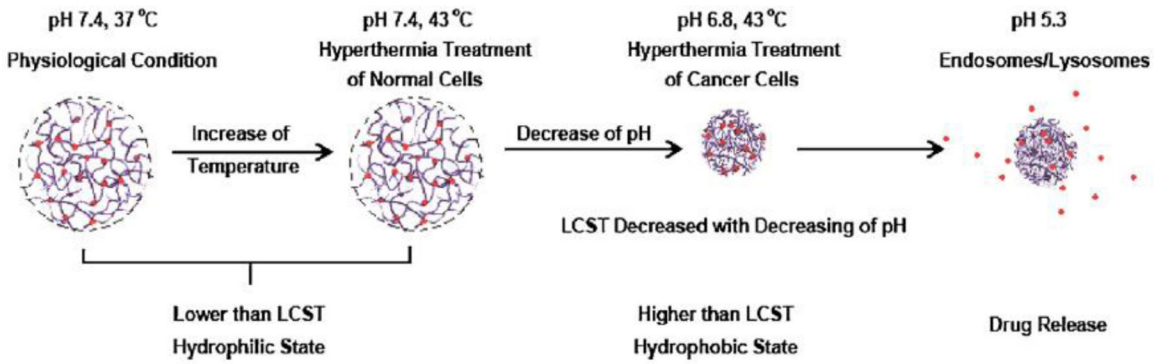


Figure 18.

Phase transition and drug release of DOX-PNA conjugates [56] Copyright American Chemical Society, reprinted with permission

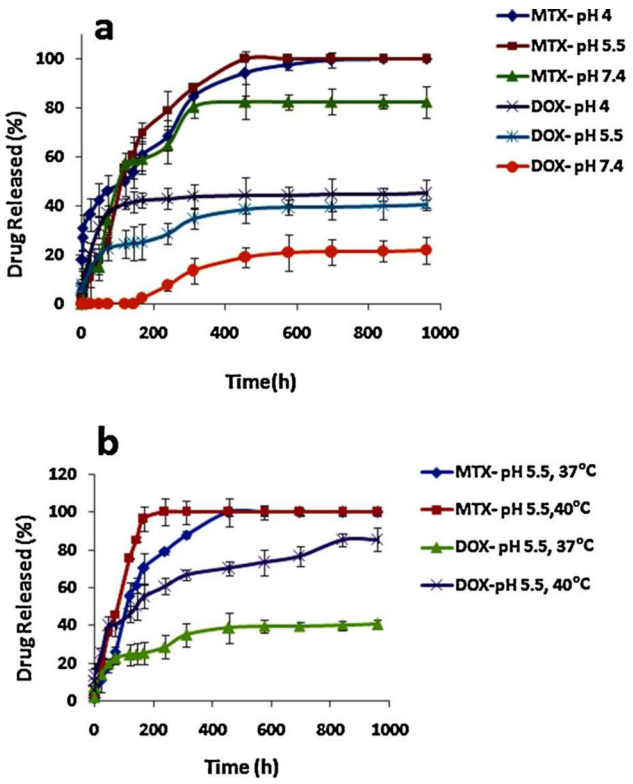
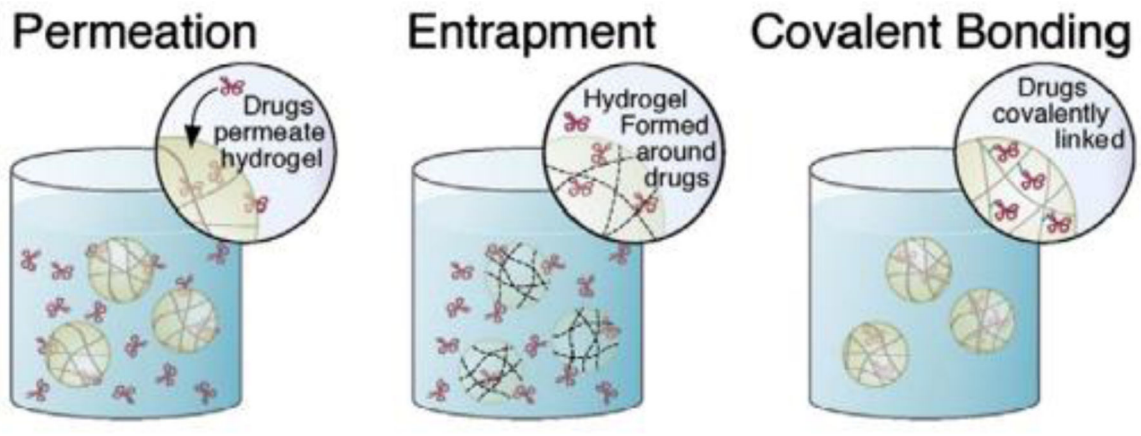
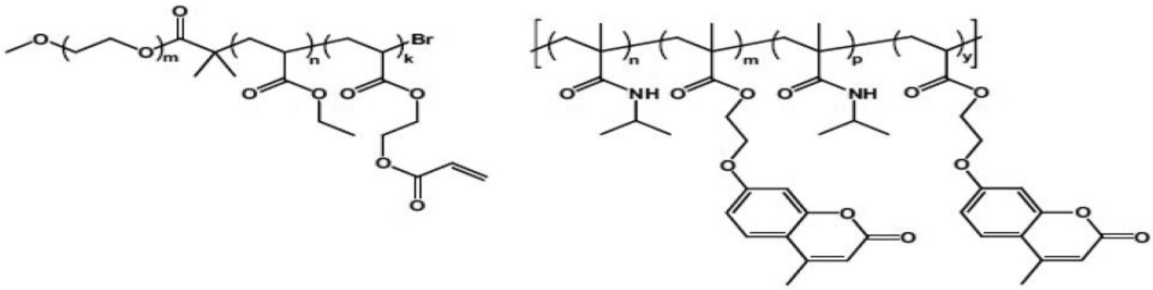


Figure 19.

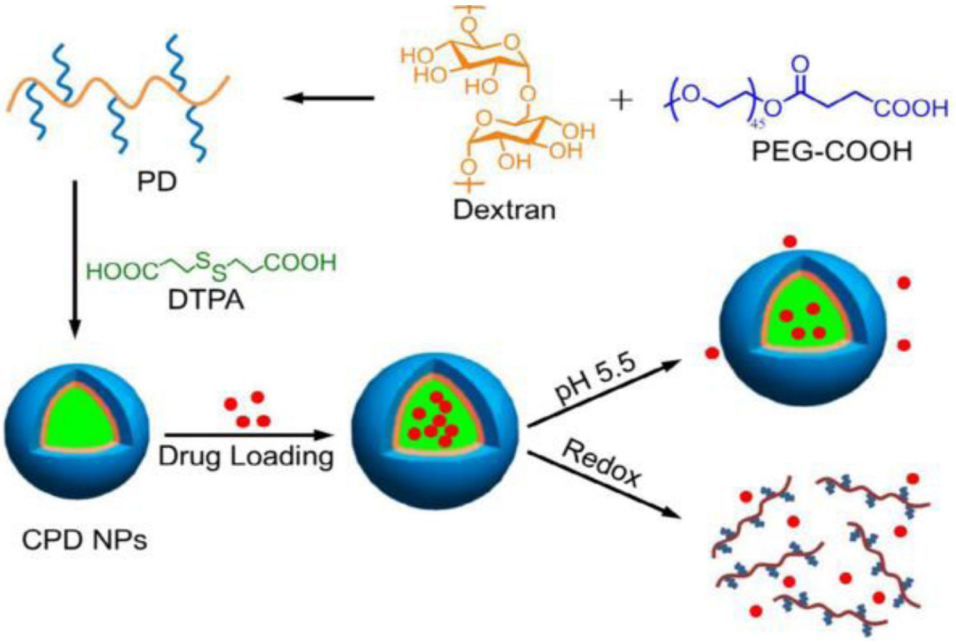
Cumulative release of methotroxate (MTX) and doxorubicin (DOX) from DOX@MTX loaded pH-responsive P(NIPAAm-MAA-DMAEMAQ) magnetic nanoparticles DOX@MTX@NIPMADM at different pH (4, 5.5 and 7.4) and different temperatures (a) 37°C, and (b) 40°C [134] Copyright Elsevier, reprinted with permission



Scheme 1.
Different methods of drug loading [58]. Copyright Elsevier, reprinted with permission



Scheme 2.
Copolymers that can be cross-linked with light [128,129]



Scheme 3.

Preparation of core cross-linked nanoparticles with pH and redox dual sensitivity [138] Copyright Elsevier, reprinted with permission

Table 1.

Classification of nanogel according to their structure

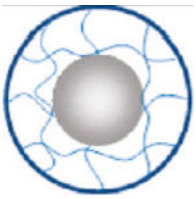
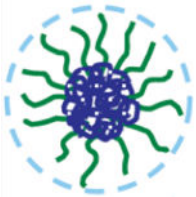
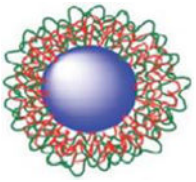
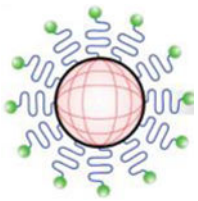
No	Type	Scheme structure	Example
1	Simple nanogel		[40]
2	Hollow nanogel		[19,41]
3	Core-shell nanogel		[42,43]
4	Hairy nanogel		[44,45]
5	Multilayer nanogel		[46]
6	Functionalized nanogel		[47,48]

Table 2.

Examples of thermo-responsive nanogels with applications for drug delivery

Nanogel composition	Drug	Site delivery	Ref.
(Fe_3O_4/P(NIPAM-co-AA))	5-fluorouraci	MCF7 cancer	[113]
HA-m-poly(DEGMA-co-CMA)	coumarin	cancer cells	[80]
Bi_2O_3@PVA	TMZ	cancer diagnostics	[114]
Poly(NIPAAm)-chitosan	Fe_3O_4	hyperthermia	[106]
NP/SiO_2/PNIPAAm	CdSe(ZnS)/SiO_2	Tissue imaging	[115]
chitosan-modified with NIPAAm	DOX	cancer	[61]
PNIPAM nanogels	L-mimicligand	Human IgG (hIgG)	[116]