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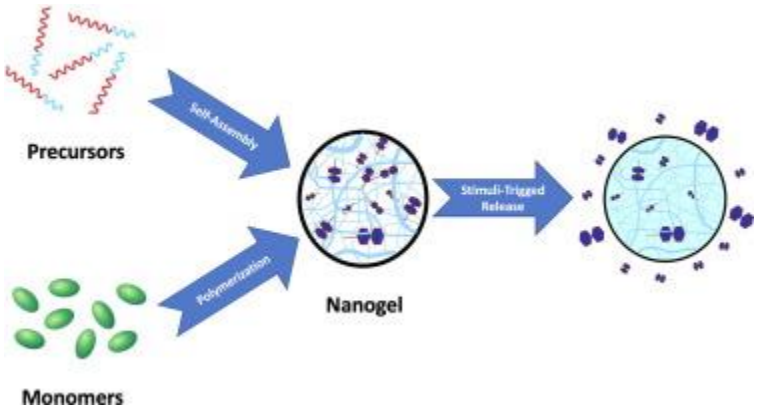
Abstract

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 and redox, thus resulting in the controlled release of loaded drugs. 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.

Statement of Significance

Smart and stimulus-responsive drug delivery is a rapidly growing area of biomaterial research. The explosive rise in nanotechnology and nanomedicine, has provided a host of nanoparticles and nanovehicles which may bewilder the uninitiated reader. This review will lay out the evidence that polymeric nanogels have an important role to play in the design of innovative drug delivery vehicles that respond to internal and external stimuli such as temperature, pH, redox, and light.



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], [4], [5], [6], [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], [9], [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], [12], [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, Shu 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].

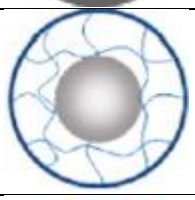
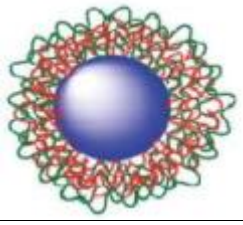
Recently, various excellent reviews on the use of stimulus-responsive nanogels have been published in the medical area [20], [21], [22], [23]. While some articles cover a diversity of different stimuli used for the release of a therapeutic moiety, some of them provide a more extensive discussion on a single specific type of stimulus such as pH-responsive, thermo-responsive, photo-responsive, or redox-responsive nanogels. Here we provide a

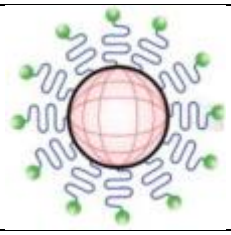
more comprehensive review of stimulus-responsive nanogels, including the mechanisms of drug release, design strategies, the type of carrier materials, and their corresponding biomedical applications such as therapy for infections, inflammatory diseases and cancer, emphasizing common challenges and recent progress in the field.

2. Synthesis of nanogels

Nanogels that have been studied in the field of drug delivery are generally formed by two types of 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 structures has been summarized in Table 1.

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]

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 features 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], [31], [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 self-assembly methods. For example, maltopentose-functionalized cholesteryl poly-L-lysine (CMaPL) was used as a macro-primer for enzymatic polymerization of branched amylose-functionalized cholesteryl poly-L-lysine nanogel for enzyme-responsive siRNA delivery (Fig. 2). The linear amylose-functionalized cholesteryl poly-L-lysine was unstable in water and formed large precipitates due to the double helix formation by the amylose chains. By contrast, the branched amylose-coated nanogel was stable due to the steric hindrance [35]. Numerous reports on physical self-assembly of nanogels in the field of drug delivery have also been published [36], [37], [38], [39].

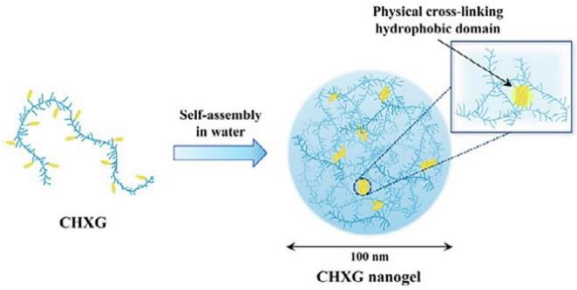


Fig. 1. Schematic representation of cholesterol-bearing xyloglucan (CHXG) nanogels. Reproduced with permission from [33].

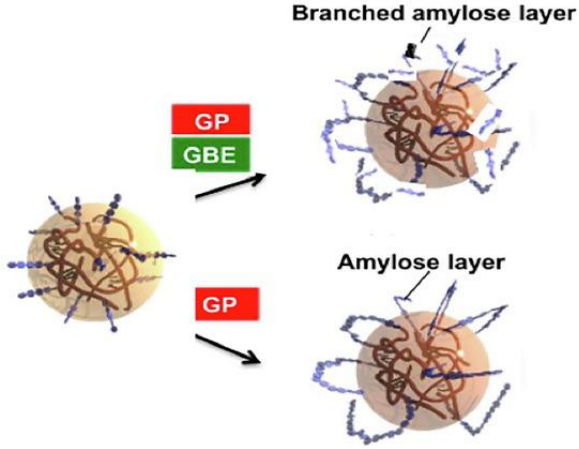


Fig. 2. Schematic illustration of enzymatic polymerizations by *sn*-glycerol-3-phosphate (GP) and *sn*-glycero-3-phosphoethanolamine (GPE) catalyzes reactions. Reproduced with permission from [35].

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 of 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 oligo(ethylene glycol) monomethyl ether methacrylate (OEOMA) in the presence of dimethacrylate (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].

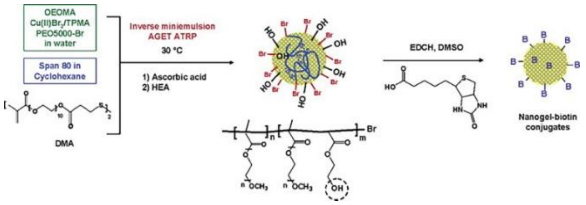
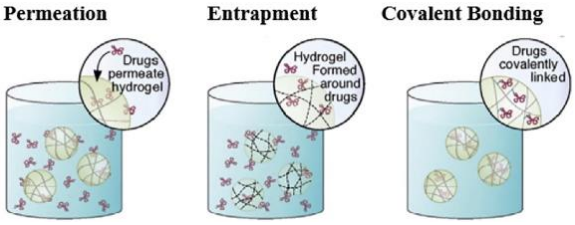


Fig. 3. OH-functionalized nanogels by ATRP in inverse miniemulsion. Reproduced with permission from [7].

3. Loading and drug release mechanisms of 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].



Scheme 1. Different methods of drug loading. Reproduced with permission from [58].

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 R_2 relaxivity, as well as the ability to be excreted by renal clearance of the disassembled nanogels (Fig. 4) [60].

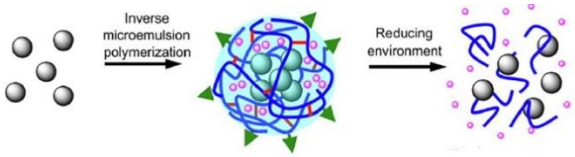


Fig. 4. Degradation of nanogel and release of drugs. Reproduced with permission from [60].

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, doxorubicin (DOX) release occurs in a thermo-responsive nanogel. By increasing the temperature of the nanogel above lower critical solution temperature (T > LCST), it collapses and the drug permeates through the polymeric shell [61].

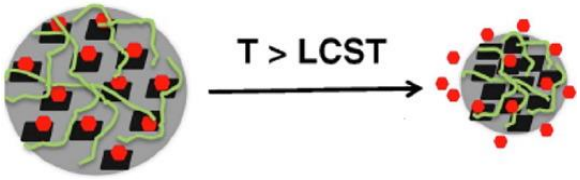


Fig. 5. Permeation release in nanogel. Reproduced with permission from [61].

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 stablity during blood circulation due to the network structure, and good biocompatibility in various medical applications [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 et al. [63] prepared biodegradable crosslinked nanogels of well-controlled using atom transfer radical polymerization (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], [70], [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/thermo-dual responsive nanogel composed of poly(N-isopropylacrylamide) P(NIPAm)-*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-isopropylacrylamide-*co*-acrylic acid) and modified with iRGD peptides to increase both the vascular and tissue permeability in a tumor-specific manner. iRGD peptides have been used to recognize their specific receptors on the targeted tumor site, and then selectively increase the drug concentration and/or the drug penetration into the tumor cells or tumor sites based on a mechanism dependent on integrin ($\alpha_v\beta_3$ or $\alpha_v\beta_5$) and neuropilin-1 (NRP-1). The iRGD motif peptides contain cyclic 9-amino peptides with the sequences (CRGD.K/R]GP.D/E]C). First, the RGD motif binds to $\alpha_v\beta_3$ or $\alpha_v\beta_5$ integrins then followed by a proteolytic cleavage and release of the C-terminal RXXR/ K sequence, also dubbed the C-terminal rule (CendR) motif, which interacts with the NRP-1 receptor. NRP-1 binding leads to triggering of an endocytic transcytosis and *trans*-tissue transport pathway that can assist drug and nanoparticle delivery, including small drug molecules, monoclonal antibodies, and nanoparticles [139], [140], [141].

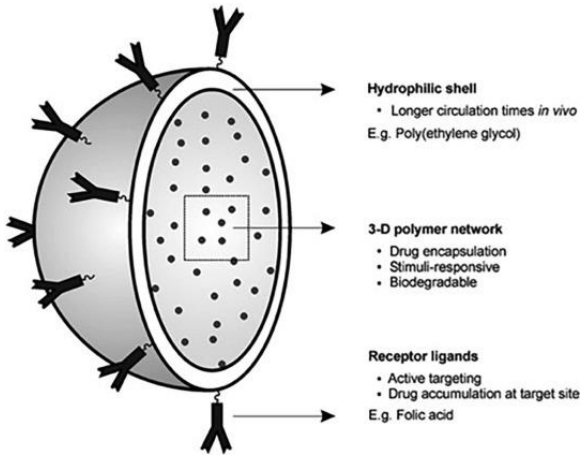


Fig. 6. Multi-functional stimuli-responsive nanogels via targeted ligands and a hydrophilic shell for clinical applications. Reproduced with permission from [74].

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], [78], [79], [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], [82], [83], [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 decreased electrostatic repulsion within the network leading to overall collapse. 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_a, 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], [86], [87], [88]. Nanogels tend to be more physically stable in physiological environments compared to other nanocarriers. Nanogels containing poly(l-Asp) derivative have been used in drug delivery systems to cause the breakdown of the lysosomal membrane by undergoing a volume change in the acidic environment, which then leads to release of many kinds of lysosomal enzymes such as phosphatases, proteases, and nucleases which can kill the neighboring host cells [89]. One study used 3-(diethylamino) propylamine (DEAP) groups that have a $pK_b \sim 6.8$ 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 (Fig. 7). 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 the size of nanogels at pH 5 decreased with increasing the amount of the poly(D,L-lactide-co-glycolide) in the nanogel. These nanogels showed significant volume expansion when the pH was reduced from 7 to 5, leading to lysosome destabilization and increased drug release [89].

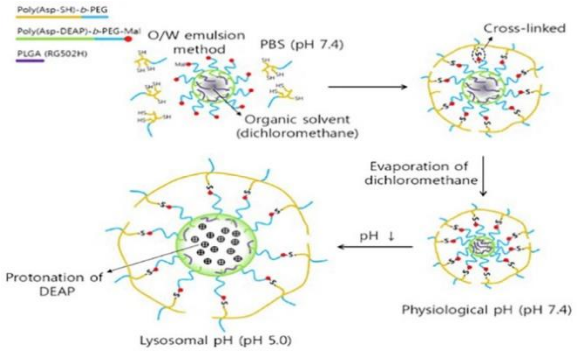


Fig. 7. Preparation of Nanogel of core-shell containing DEAP groups. Reproduced with permission from [89].

Fig. 8 shows that the tumor-targeting of nanogels was successfully carried out by neutralization of the lysosomal pH using nanogels with lysosomotropic amines [89].

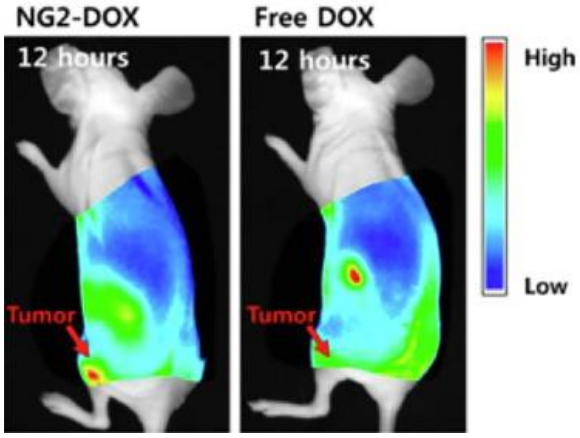


Fig. 8. Non-invasive fluorescent imaging of uptake DOX-loaded nanogels or free DOX injected into tumor-bearing nude mice. Reproduced with permission from [89].

Many similar studies also report the construction of pH-responsive nanogels. For example, Liechty 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 [90], [91]. The results showed that P(DEAEMA-co-TBMA-*g*-PEGMA) nanogels with an increasing t-butyl methacrylate (TBMA) content, reached a maximum swelling volume at pH 5.50, but in poly(2-(diethylaminoethyl)methacrylate-*co*-(t-butylaminoethyl methacrylate)-*co*-poly(ethylene glycol) methyl ether methacrylate) (PDEAEMA-co-TBAEMA-*g*-PEGMA) nanogels (due to the presence of several species of ionized groups) many changes were not observed. Therefore, they suggested that (PDEAEMA-*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 [92], [94], [95]. Brannigan et al. [96] 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).

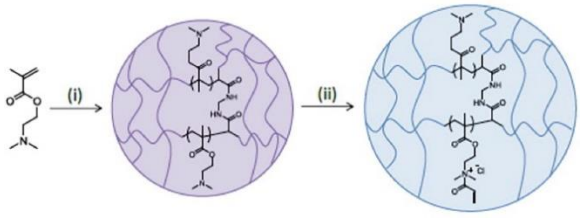


Fig. 9. Synthesis of quaternized (PDMAEMA) nanogels. Reproduced with permission from [96].

Due to the relatively inefficient targeting ability of some nanogels that rely solely on the enhanced permeability and retention (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 [97].

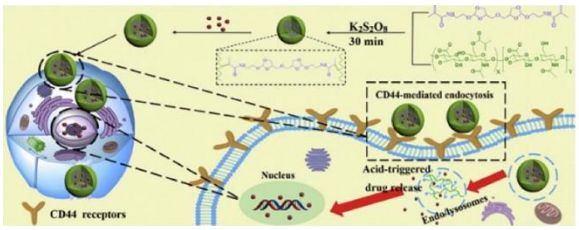


Fig. 10. Scheme of the targeted DOX release from pH-triggered HA-NGs. Reproduced with permission from [97].

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 to 45 °C [98], [99]. 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).

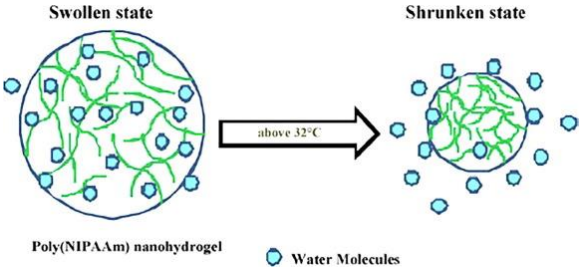


Fig. 11. Temperature-responsive nanogel encapsulating Fe_3O_4 nanoparticles and its release of water molecules in response to increased temperature. Reproduced with permission from [104].

Temperature-sensitive nanogels show a response to a temperature near physiological temperature. For instance, poly(N-isopropylacrylamide-*co*-acrylic acid) P(NIPAm-*co*-AAc) 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 and 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 [100].

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 [101]. 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 [102], [103].

The positive temperature sensitivity of the polymer hydrogel is defined by a upper 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 [105], [106]. The epidermis and stratum corneum of the skin acts as an effective barrier to prevent penetration of topically applied drugs. Preparing nanogels by a hydrogen-bonded layer-by-layer (LbL technique), controls the chemical composition, nanoscale thickness, mechanical properties and converts a burst release mode to a sustained release mode [107], [108]. Zavgorodnya et al. [109] investigated the loading behavior and release of the sodium diclofenac drug cargo in poly(N-vinylcaprolactam-co-acrylic acid) ((<nu > PVCL)$_{30}$-AAD) nanoparticles core-shell based nanothin temperature-responsive hydrogel films, that were prepared by the LbL hydrogen-bonded technique. The results showed that the release of sodium diclofenac above the LCST of the polymer (LCST ~ 32 °C) was higher than at 25 °C (Fig. 12A). Also, they showed the effect of DMSO (a penetration enhancer) on (<nu > PVCL) $_{30}$-AAD, and demonstrated that the formulation of (<nu > PVCL) $_{30}$-AAD with DMSO reduced the delay time and increased the amount of transported drug at 32 °C over 25 °C, in comparison to not using DMSO (Fig. 12B).

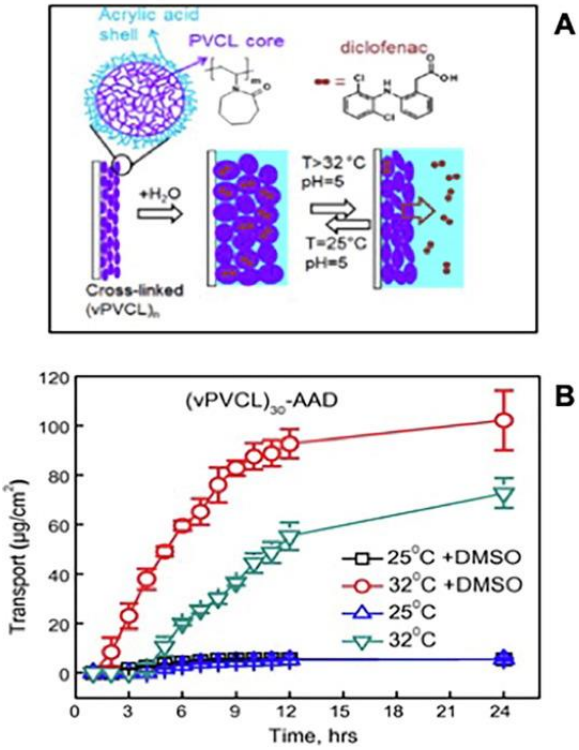


Fig. 12. Temperature-responsive (<nu > PVCL) and release behavior of drug (A),Transport of diclofenac from the ((<nu > PVCL)$_{30}$-AAD) nanohydrogel with or without DMSO at two different temperatures: 25 and 32 °C (B). Reproduced with permission from [109].

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, then synthesized varying compositions of P(NIPAm) and the ratio of NIPAm/N-(isopropylmethacrylamide) (NIPMAm) 1:1P(NIPMAm$_{50}$) with as a shell to form core-shell nanogels, and investigated the drug release behavior at different temperatures. 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 from a 1:1 mixture of P(NIPAm) and P(NIPMAm50) nanoparticles more slowly than pure P(NIPAm) nanoparticles due to retention of the drug by P(NIPMAm50) at 37 °C. Upon increasing the temperature to 43 °C, the nanoparticle mixture showed an improved drug-release profile due to additional release of DOX from P(NIPMAm50). As such, the nanoparticle mixture provided a more sustained release of DOX than individual nanoparticles, thereby enhancing the cell-killing effect of the drug (Fig. 13) [110]. There is a wide range of polymeric nanogels that exhibit a LCST around the physiological temperature (Table 2).

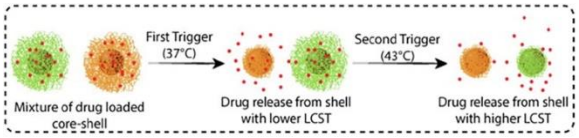


Fig. 13. Temperature-dependent release of a drug from a nanogel in varying conditions. Reproduced with permission from [110].

Table 2. Examples of thermo-responsive nanogels for drug delivery applications.

Nanogel composition	**Drug**	**Site delivery**	**Ref.**
(Fe_3O_4/P(NIPAm-co-AA))	5-fluorouracil	MCF7 cancer	[111]
HA-m-poly(DEGMA-co-CMA)	coumarin	cancer cells	[80]
Bi_2O_3@PVA	temozolomide	cancer tumors	[112]
PVCL-co-AA	diclofenac	skin	[104]
κ-carrageenan	methylene blue (as a model drug)	cancer cell	[113]
chitosan-modified with P(NIPAm)	DOX	cancer	[61]
poly(L-lactide)-g-pullulan	(DOX)	cancer	[114]

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], [115], [116]. 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 [117]. Noree et al. [118] formed amphiphilic random copolymers consisting of poly(pentafluorophenyl methacrylate)-*co*-polyoligo(ethylene glycol methacryl amide) (PPFPMA-*co*-POEGMAM) by post-polymerization modification, then after self-assembly into micelles, the addition of cystamine as a cross-linking agent produced redox-responsive nanogels. During the formation of the micelles, they encapsulated a model hydrophobic drug (NR) inside, and examined the release behavior in the presence and absence of GSH (Fig. 14A and B).

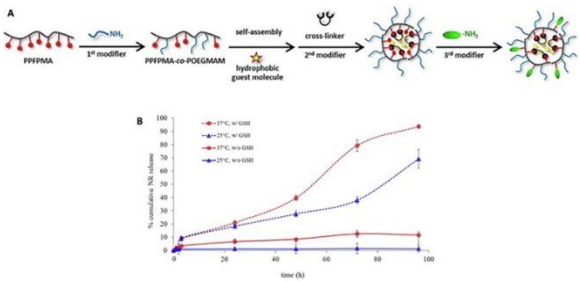


Fig. 14. post-polymerization modification of PPFPMA with amine modifiers toproduce a redox-responsive nanogels (A), NR release profiles from nanogels in presence and without GSH (B). Reproduced with permission from [118].

Recently, a new bio-reducible DOX-loaded cross-linked dextrin nanogel (DNG) covered with AMD3100 was used with multifunctional properties such as targeting by CXCR4 chemokine, intracellular release of DOX, and prevention of tumor metastasis (Fig. 15). The anti-metastatic and anti-tumor activity in vivo is shown in Figure (16A-B). The tests showed decreased lung metastasis and inhibition of tumor growth by DOX. Therefore, efficient inhibiton of tumor metastasis was stronger with the DOX-AMD-DNG nanogels than the free AMD3100 (Fig. 16A). Histopathological (H&E) staining was used to investigate the DOX-AMD-DNG anti-tumor efficacy (relative to other formulations) on lung tissue and tumor segments in Balb/C mice. The results showed that there was no significant changes in the tumor metastases and cancer growth in groups treated with free AMD3100, free DOX only inhibited tumor growth, while DOX-AMD-DNG repressed both the breast cancer growth and lung metastasis synergistically (Fig. 16B) [119]. Lee et al. [120] investigated the encapsulation of 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 [121], [122].

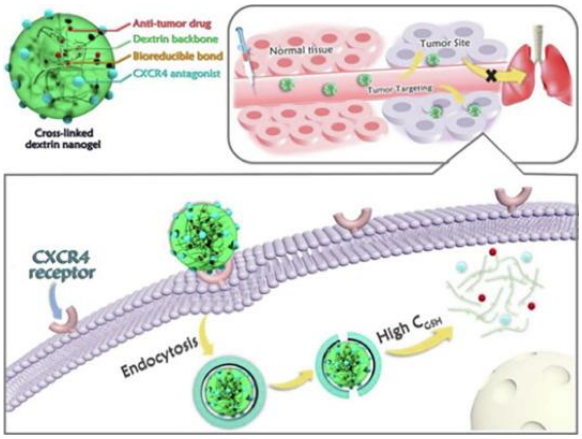


Fig. 15. Schematic illustration of controlled release by CXCR4–ligand modified DOX-encapsulated dextrin nanogel at the tumor site. Reproduced with permission from [119].

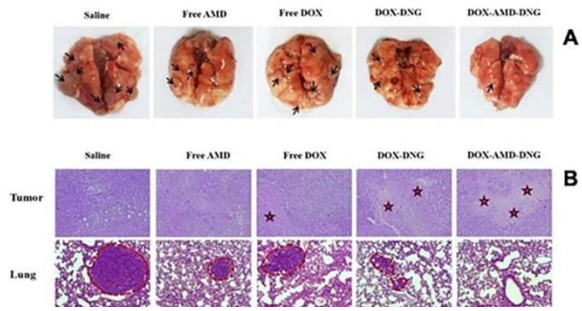
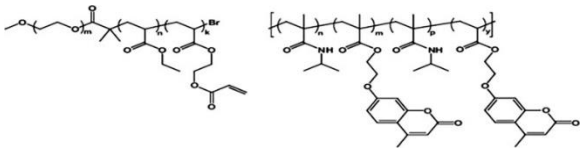


Fig. 16. Saline effects, free AMD, free DOX, DOX-DNG and DOX-AMD-DNG on mouse lung. The efficacy of the formulations on the lung metastasis in mice (black arrows indicate the metastatic foci) (A). H&E analysis showing tumor and lungs of mice treated with various formulations (stars and red circles indicate cancer cell remission and tumor metastases to the lung, respectively) (B). Reproduced with permission from [119]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

6.4. Light-responsive nanogels

Near-infrared (NIR) light with wavelengths in the range of 650–900 nm has recently been used as a stimulus to trigger drug release, with advantages such as mild reaction conditions, high biocompatibility, ability for in-situ polymerization for specific applications and lower toxicity. Moreover, the photoreaction can also be reversible.

NIR radiation can penetrate deeper than 10 cm into tissue under some circumstances [123], [124], [125]. Photo-responsive polymeric nanogels often contain acrylic or coumarin-based bonds that cleave under illumination causing drug release (Scheme 2) [126], [127].



Scheme 2. Copolymers that can be cross-linked with light. Reproduced with permission from [126], [127].

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 [128]. Hyaluronic acid (HA) 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 HA receptor known as CD44, which is a high affinity HA receptor that is over-expressed on various cancer cells [129]. 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 very high two-photon absorption cross-section leading drug release by either NIR (2-photon) or UV (1-photon) triggers. 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) [130].

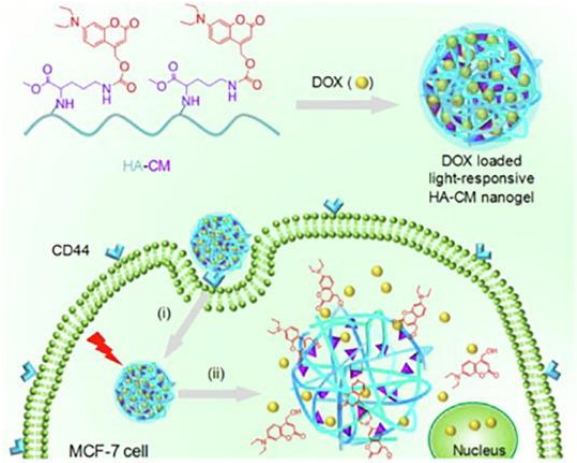


Fig. 17. Light-responsive HA-CM nanogels for CD44 targeted and remotely controlled DOX delivery. (i) Receptor-mediated endocytosis, and (ii) nanogel swelling and drug release upon light irradiation. Reproduced with permission from [130].

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. [125] 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].

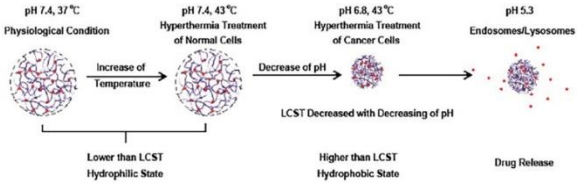


Fig. 18. Phase transition and drug release of DOX–PNA conjugates. Reproduced with permission from [56].

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 [131]. In one study, dual temperature/pH-sensitive superparamagnetic nanogels were fabricated with temperature-responsive poly(N-isopropylacrylamide) P(NIPAm) 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. 19a and b) [132].

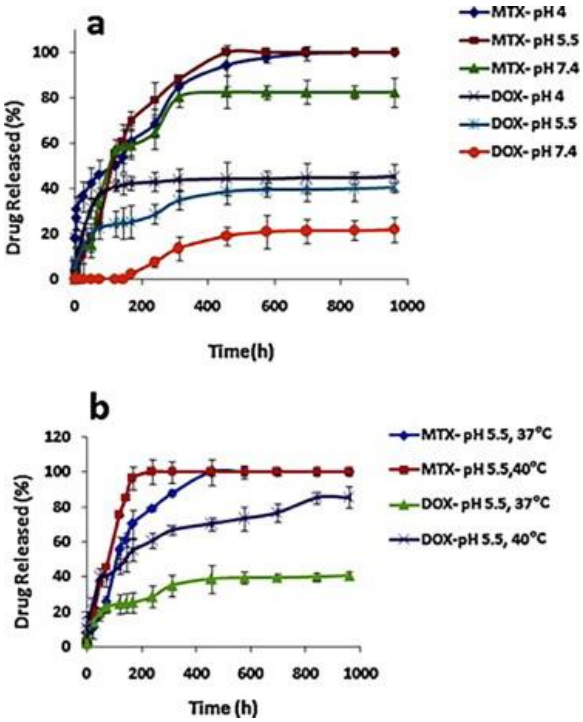
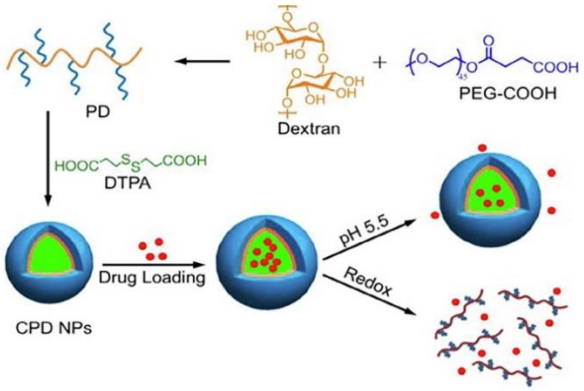


Fig. 19. Cumulative drug release of DOX@MTX from P(NIPAm-MAA-DMAEMAQ) magnetic nanoparticles at different pH values (4, 5.5 and 7.4) and different temperatures (a) 37 °C, and (b) 40 °C. Reproduced with permission from [132].

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 of acrylic acid (AAc) and 2-methacryloylethyl acrylate (MEA) units, with another chain either alone or as both poly(N-isopropylacrylamide) P(NIPAm) 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 [133]. In another study, Jin et al. [134] demonstrated the drug-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) [135]. Recently, Lian et al. prepared core cross-linked 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).



Scheme 3. Preparation of core cross-linked nanoparticles with pH and redox dual sensitivity. Reproduced with permission from [136].

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 DTPA cross-linker, the rate of release increased [136]. 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 [137]. 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 $HepG_2$ 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 [138].

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,

NH2, 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 for cancer chemotherapy and can also be used for imaging reporter molecules.

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Disclosures

Dr Hamblin is on the following Scientific Advisory Boards
Transdermal Cap Inc, Cleveland, OH
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Johnson & Johnson Inc, Philadelphia, PA
Sanofi-Aventis Deutschland GmbH, Frankfurt am Main, Germany
Dr Hamblin is a stockholder in
Global Photon Inc, Bee Cave, TX
Mitonix, Newark, DE.

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