Multi-responsive micro/nanogels for optical sensing

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ABSTRACT

Micro/nanogels are unique materials that exhibit the properties of both colloids and hydrogels, i.e. being colloids they exhibit a large specific surface area, while they are hydrophilic and porous allowing them to swell to a great degree with water. Engineering micro/nanogels, through the rational design of various polymer compositions and/or optical structures, can enable them to respond to a myriad of stimuli, e.g. temperature, pH, biomolecules, CO2, light, and electricity. These multi-responsive micro/nanogels and their assemblies, are capable of recognizing and transducing analyte signals into changes in optical properties observable spectroscopically or via the naked eye, allowing their use as optical sensors. In this review, we have highlighted recent state-of-the-art examples of stimuli-responsive micro/nanogel-based systems for optical sensors.

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Introduction

The color of objects is a characteristic that can be attributed to the wavelength of light they emit, reflect, and/or absorb [1–3]. Color can be described using three parameters: hue (dominant wavelength), saturation (chromatic purity) and brightness (photon intensity). In everyday life, colors help us identify objects and their environments via different variations and combinations of these three parameters. The various interactions between light and materials have been of considerable interest to society, resulting in significant advances in photophysical technologies such as lighting [4], photography [5], telecommunication [6], imaging [7] and optical instruments [8]. Such interactions can be sensitive enough to track physical and/or chemical changes in the environment, and these interactions can also be used to develop various novel optical sensors [9].

Micro/nanogels are micro-to-nano-sized colloidal particles composed of a crosslinked network of water soluble/swellable polymers, which have found applications in various areas, including encapsulation, tissue engineering, and controlled delivery [10,11]. Generally, micro/nanogels in the water swollen state scatter little light, and their solutions appear transparent. Thus, additional chemistry is required to equip micro/nanogels with the ability to respond to light, and to produce changes in color. Copolymerization or post-polymerization modification of micro/nanogels with chromophores and/or luminophores are the most common approaches to colorize micro/nanogels. The color observed from chromophores is derived from the ‘reflectance’ of complementary wavelengths of visible light being absorbed. In comparison, the color from luminophores stems from emitted photons that are generated by absorption of photon energy, a concomitant energy level transition, and electron relaxation. Looking to colors observed in nature, such as the wings of a butterfly, opal gemstones, and beetles, another widely-studied phenomena, called structural coloration, emerges [12–14]. Unlike chromophores or luminophores, structural color is a result of visible light wavelengths undergoing constructive/destructive interference upon interaction with the ordered/periodic structure of a material. When micro/nanogels are used as the structural features in such materials, the wavelengths of light that are reflected depend on the size of the micro/nanogels, and their center-to-center distance. An interesting feature of micro/nanogels is their ability to be rendered stimuli-responsive, i.e. they can be modified chemically to allow them to change size and/or refractive index in response to specific stimuli. The modification or copolymerization of signal recognition units, such pH-sensitive units, thermosensitive agents, dyes/luminophores, chelating groups, enzymes/DNA, can endow micro/nanogels with desired selectivity. As a result, when micro/nanogels change their size and/or refractive index, the
materials reflect different wavelengths of light, and hence exhibit different colors. Specific stimuli include: pH [15,16], light [17,18], temperature [18], metal ions [19], and biomolecules [20].

In this review, stimuli-responsive micro/nanogel-based ‘etalons’ as a specific class of optical sensing devices will be discussed first. Subsequently, the focus will be on micro/nanogels that are modified by, or loaded with, small molecules and nanomaterials. Throughout all the topics addressed in this review, we will highlight the process of analyte recognition and subsequent optical signal transductions.

**Etalon-based optical sensors**

Photonic materials exhibit optical properties, such as color, as a result of their single- or multi-dimensional structural periodicity. As mentioned above, butterfly wings and opals are colored due to this phenomenon [21]. Fabry-Perot etalons are photonic materials that exhibit characteristic optical properties due to their structure, composed of a dielectric material sandwiched between two thin reflective films/mirrors. Changes in the distance between the two mirrors results in predictable changes to the optical properties, such as the wavelengths of light reflected from the etalons, which can be observed as a color change of the device.

The Serpe Group has generated etalons using poly(N-isopropylacrylamide)-based (pNIPAm) microgels as the dielectric layer [22]. That is, by ‘sandwiching’ a monolithic layer of pNIPAm-based microgels between two thin Au layers/mirrors, devices with tunable optical properties could be constructed (Figure 1A) [22]. Incident light entering the optical cavity formed between the two Au mirrors undergoes

![Figure 1](image-url)

**Figure 1.** (A) Structure of an etalon device with (a, c) two Au-films ‘sandwiching’ a monolithic layer of (b) pNIPAm-based microgel particles on a (d) glass substrate. (B) Characteristic multi-peak spectra for etalons assembled with pNIPAm-co-AAc microgels and the visually observable color of the etalons in the (f) hydrated and (k) dry state. Reprinted with permission from ref [23]. Wiley, 2011.
interference resulting in specific wavelengths of light being reflected that can be observed spectroscopically and/or visually (Figure 1B). The reflected wavelength maxima can be predicted by Equation 1.

\[ \lambda m = 2nd \cos \theta \]

Where \( \lambda \) is the position of the peak in the reflectance spectrum, \( m \) is the peak order, \( n \) is the refractive index of the microgel (dielectric) layer, \( d \) is the distance between the two Au films and \( \theta \) is the angle of observation. For a given peak order, equation 1 shows that \( \lambda \) is directly proportional to \( d \), i.e. modulation of the distance between the two Au layers can shift \( \lambda \). The optical property changes imparted upon etalons by the reversible solvation state changes of pNIPAm-based microgels in response to external stimuli has been exploited in numerous studies by the group [18-22-29].

Early publications from the group focused on establishing the basic function of the microgel-based etalons. For example, etalon devices assembled with pNIPAm-based microgels copolymerized with various functional comonomers could render the microgels responsive towards stimuli other than the inherent temperature responsivity of pNIPAm-based microgels [17,30]. Etalon devices assembled with pNIPAm-based microgels copolymerized with acrylic acid (AAc) (pNIPAm-co-AAc) have shown temperature and pH-dependant changes in their optical properties [22,30]. AAc copolymerization also has an added utility as a handle for further chemical modification of microgels, thus expanding the potential applicability of microgel-based etalons for sensing.

In another example, pNIPAm-co-AAc microgels were modified with ferrocene for sensing H₂O₂ in solution. Sensing H₂O₂ in biological samples is of great importance due to its function as a regulator of many physiological processes and its role as a by-product in many biological reactions. Etalons assembled using ferrocene-modified microgels showed a reflectance peak blue shift in response to H₂O₂ due to oxidation of the Fe²⁺ in ferrocene to Fe³⁺ and the subsequent interactions between the polar amide groups in pNIPAm and the Fe³⁺. It was shown that the position of the etalon’s reflectance peak was proportional to the concentration of H₂O₂ present in the sample and the limit of detection (LOD) was calculated to be around ~40 µM. Given that H₂O₂ is a by-product of many enzymatic reactions, the utility of this approach as an indirect method for monitoring biological analytes such as glucose was shown using the oxidation of glucose in the presence of glucose oxidase enzyme [31].

Recently, the group reported on the use of microgel-based etalons for the detection of volatile organic compounds (VOCs) in water. VOCs, e.g. tetrahydrofuran (THF), are hazardous when dissolved in water, and can have severe negative impacts on aquatic life [24]. This study demonstrated that etalons assembled with microgels consisting of 95% pNIPAm,
crosslinked with 5% N,N’-methylenebis(acrylamide) (BIS), exhibited a reflectance peak blue shift when THF vapor was bubbled through the aqueous solution they were immersed in (Figure 2A). Cononsolvency of pNIPAm-based microgels in THF-water mixtures was proposed as the mechanism of the etalon response. A linear relationship (Figure 2B) between reflectance peak shift and the amount of THF bubbled through the experimental setup was obtained with a LOD of 1.27 mM of THF, detected within 4 min. Furthermore, it was shown that the LOD could be improved by modulating the experimental parameters, such as the vapor flow rate and vapor bubble size.

Etalon devices that exhibit responsivity to CO₂ dissolved in water were assembled using pyridine-containing microgels [26]. Specifically, when CO₂ gas was dissolved in water H₂CO₃ was formed, which can protonate the microgels’ pyridine groups forming charged pyridinium ions (Figure 3A).

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**Figure 2.** (A) Experimental setup for studying the etalon response to vapour phase VOCs. (B) Absolute total peak shift recorded in response to different volumes of THF being bubbled through the experimental system showing a linear response. Reprinted (adapted) with permission from ref [24]. Copyright 2019, Elsevier.

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**Figure 3.** (a) Schematic diagram depicting the response mechanism of the etalon to CO₂. (b) Response of an etalon assembled with microgel containing 60% pNIPAm and 25% 4-vinylpyridine, crosslinked with 5% BIS to repeated CO₂ and N₂ exposures. Reprinted (adapted) with permission from ref [26]. Copyright 2015, Royal Society Chemistry.
The resultant Coulombic repulsion between the polymer chains in the microgels induces swelling, which was observed spectroscopically as a reflectance peak red shift. It was shown that the extent of CO$_2$ response could be modulated by controlling the amount of pyridine groups incorporated into the microgel, with higher pyridine content resulting in a larger overall response and that the etalon response could be reversed by bubbling N$_2$ gas through the reaction solution (Figure 3B).

Biomolecule sensing with pNIPAm-based etalons has also been extensively studied by the Serpe Group. Etalon-based optical sensing systems have been prepared for sensing antibodies [32], steroid hormones such as β-Estradiol (E2) [33] and progesterone (P4) [34], proteins [28] and ssDNA [29]. Recently, the group reported that etalon devices assembled with microgels containing pNIPAm copolymerized with acrylic acid (pNIPAm-co-AAc), and modified with polyclonal anti-P4 antibodies could be used to quantify ng/mL levels of P4 in aqueous solutions. P4 binding to the antibody-modified microgels induced crosslinking in the microgel network, leading to a collapse of the microgel particles which manifests as a reflectance peak blue shift. To demonstrate the selectivity of this approach the sensor was shown to have a low cross reactivity to E2, a common interferent when it comes to P4 detection. This study demonstrated the versatility of this approach by using two different anti-P4 antibodies and showed that the same approach could potentially be used for the detection and quantification of a wide array of antigens, just by using the appropriate antibodies for microgel modification [34].

Furthermore, an optical sensor for detecting picomolar levels of E2 was developed by using an aptamer-modified etalon device assembled from pNIPAm-co-AAc microgels [33]. In this work, disulfide-modified aptamers were reduced to form a thiolated aptamer and subsequently applied on to the top Au layer of the etalon device. Aptamers can be chemically engineered to undergo a change in their conformation from a more linear state to a more compact state upon binding their targets (Figure 4). The sensing mechanism of this work exploits this change of conformation as a means to block the diffusion of Na$^+$ or Ca$^{2+}$ ions into the etalon device. Cation diffusion into the microgels can induce a collapse in the microgel network by neutralization of the charged AAc moieties, yielding a spectroscopic blue shift. Therefore, an etalon exposed to a high concentration of E2 would exhibit a smaller blue shift in a given time compared to an etalon exposed to a lower concentration of E2. We hypothesize that this is a direct result of more surface pores being blocked by the aptamer bound to E2 than at low concentration, which allows easier entry of the ions into the microgel layer. Specificity of the device was also investigated by observing the response to P4, the response from 10 ng/mL of P4 was significantly less than that from 5 pg/mL E2, indicating the device was selective towards E2.
In addition to the studies discussed in this section, we have demonstrated that the etalon-based sensing systems are capable of sensing a myriad of other analytes including ethanol in gasoline [25], glucose [27] and polyelectrolytes [35].

**Micro/nanogels modified with small molecules**

Micro/nanogels can be functionalized with fluorescent molecules for the purpose of optical sensing. Typical fluorophores include: azobenzene [36], spiropyran [37], coumarin [38], and a variety of others [39,40]. The fluorescence of the micro/nanogels can be ‘turned on’ or ‘turned off’ triggered by the physical/chemical interactions between the analytes of interest and the fluorescent probes, and/or the interaction between fluorophores mediated by the solvation state of the micro/nanogels. Consequently, the type and/or concentration of analytes can be easily determined by measuring the change in fluorescence intensity, both visually and/or spectroscopically. So far,
micro/nanogel-based fluorescence sensors have been developed for detecting temperature and pH [41,42], metal ions [43,44], strain [42], and reactive oxygen species (ROSs) in vivo [45].

Fluorescent molecules can simply be embedded within the gel matrix by physical entrapment/encapsulation, however leaching of fluorescent molecules from the gel is practically unavoidable. Therefore, fluorescent molecules are typically bound to gels through covalent attachment, effectively solving the leaching problem. One feasible strategy is to modify fluorescent molecules with unsaturated carbon-carbon double bonds [38,46,47]. For example, O’Reilly and coworkers designed amino-bromomaleimide (ABM)-labelled microgels where ABM was covalently attached through the copolymerization of ABM methacrylate, with ABM located in the gels’ hydrophobic core [46,47]. While bubbling CO₂ gas into solution, microgels were highly swollen, this is due to the protonation of the tertiary amines of poly(N, N,-diethylaminoethyl methacrylate) (pDMAEMA). This increased the microgel hydrophilicity and led to a decrease in fluorescence. After simply purging N₂ gas into the solution, the microgels collapsed, and the fluorescence intensity recovered. As a result, ABM-labelled microgels were able to respond to the hydrophilicity/hydrophobicity of the microgels’ core and the size of the microgels. Fluorescent molecules can also be used as crosslinkers in the gel matrix. For example, Zhu et al. reported pNIPAm microgels that were crosslinked with di-chlorinated 1,1'-di[4-(vinyl)benzyl]-4,4'-pyridinium salt (MSPC²⁺ 2Cl⁻), which rendered the gels with optical sensing ability. MnO₄⁻ anions induced significant fluorescence quenching of the pNIPAm-MSPC microgels. They found that the fluorescent sensor was able to detect trace MnO₄⁻ anions in aqueous solutions with a fast response time of 5 min [44].

The abovementioned systems relied on monitoring fluorescence intensity at a single wavelength, however, such a strategy is easily affected by many factors, e.g. environmental noise, and fluctuations in the light source intensity, among other things [48]. As a result, micro/nanogel-based ratiometric fluorescence sensors have been developed. For instance, a colorimetric fluorescent poly(acrylamide-co-N-(3-aminopropyl)methacrylamide) (pAAm-co-APMA) nanogel sensor was reported for detecting X-ray dosages. Under exposure to X-rays, 5(6)-carboxytetramethylrhodamine is stable, and emits red fluorescence (I₅₄₆). Alternatively, coumarin-3-carboxylic acid, when exposed to X-rays, transitioned to 7-hydroxyl-coumarin-3-carboxylic acid, which emitted blue fluorescence under UV irradiation (I₄₀₅). Consequently, the dose of X-rays can be determined by measuring the ratio of I₄₀₅ and I₅₄₆ [38]. In another example, Yin et al. prepared ratiometric fluorescent K⁺ sensors that are based on pNIPAm microgels covalently
incorporated with K$^+$-recognizing 4-acrylamidobenzo-18-crown-6 residues (B18C6Am), fluorescence resonance energy transfer (FRET) donor dyes (i.e. 4-(2-acryloyloxyethylamino)-7-nitro-2,1,3-benzoxadiazole (NBDAE)), and rhodamine-B-based FRET acceptors (RhBEA) [49]. When the spectra of donor emission and acceptor absorption overlap, and the distance between the donor and acceptor is less than 10 nm, non-radiative energy transfer occurs. Under this condition, excited-state energy is transferred from the donor to the acceptor, resulting in fluorescence from the acceptor. In this case, when the temperature was increased above the lower critical solution temperature (LCST) of pNIPAm, the p(NIPAm-B18C6Am-NBDAE-RhBEA) the microgels collapsed, generating a FRET effect due to the reduced distance between the donor and acceptor. The addition of K$^+$ ions in solution can lead to the reswelling of initially collapsed microgels. This is because the B18C6Am can capture K$^+$ ions, resulting in the enhancement of microgel hydrophilicity and elevated LCST temperatures. Thus, the fluorescence intensity from the acceptor decreased. Using the FRET concept, Zhu et al. synthesized poly(methyl methacrylate-co-methacrylic acid-co-(9-phenanthryl)methyl methacrylate-co-(9-anthryl)methacrylate (pMMA-co-MAA-co-Ph-co-An) nanogels for determining solution pH [42]. When pH < pKa of MAA, the protonated -COOH groups cause the nanogels to deswell. Therefore, the donor (Ph) and acceptor (An) are very close to each other, exhibiting enhanced fluorescence signal from the acceptor (An). As pH increased above the pKa of MAA, the -COOH groups were deprotonated, resulting in the swelling of the gels. This process increased the distance between the donor (Ph) and acceptor (An), hence the fluorescence intensity from the donor (Ph) was increased (Figure 5) [42].
**Micro/nanogels doped with nanomaterials**

Besides the direct modification of micro/nanogels with small molecules to achieve multi-responsive properties for optical sensing, an alternative approach involves the incorporation of nanomaterials into the gels. Owing to the porous structure of micro/nanogels, a variety of nanomaterials, including nanoclusters [50], nanorods [51], nanosheets [52], metallic nanoparticles [53–60] and quantum/carbon dots [61–63], can be successfully embedded into the polymeric matrix via facile methods, without interfering with the transport process between the nanomaterials and the outside environment. The multi-responsive properties can, therefore, be obtained by this unique multi-component structure via the synergistic effect of each component’s stimuli-responsivity in those hybrid systems, i.e. the incorporated nanomaterials can respond to some specific stimuli whereas the polymeric micro/nanogel matrix can be sensitive to other stimuli [63,64]. Beyond achieving multi-stimuli responsivities, providing the embedded nanomaterials with the polymeric micro/nanogel matrix also offers other advantages, such as tunable physicochemical properties, increased stability in the sensing environment, improved biocompatibilities (which is critical in biologically relevant settings and clinical applications), as well as enhanced optical signals, compared to using nanomaterials or micro/nanogels alone. Due to these advantages, over the past few years, nanomaterial-incorporated micro/nanogels have seen an upsurge as optical sensing platforms/devices for various fields [18,33,51,55,62,63]. In this section, some recent examples of multi-stimuli responsive optical sensing strategies using nanomaterial-incorporated micro/nanogels, especially focusing on metallic nanoparticles [56] and carbon dots-incorporated nano/microgels [63] will be discussed.

Metallic nanoparticles, especially silver and gold nanoparticles (AgNPs and AuNPs, respectively), are ideal choices for optical sensing applications [65,66] due to their unique size-dependent optical properties, facile synthetic procedures, and versatility/simplicity of chemical modification. A wide range of optical sensors based on AgNP- or AuNP-incorporated micro/nanogel have been studied and developed over the past few years, including several examples from the Serpe Group [18,53,54]. Even so, the versatility and practicality of such hybrid systems deems them worthwhile of further discussion here. For example, as shown in Figure 6, Li et al. developed a core-shell structured, multi-stimuli-responsive nanoprobe where AuNPs were contained in nanogels, to achieve in vivo imaging of caspase activity [56]. They first prepared AuNPs covered with Cy5-labeled, caspase-degradable peptide (pep-AuNPs), which resulted in the quenching of fluorescent Cy5 dyes due to the FRET effect between Cy5 and AuNPs. Next, they synthesized AuNP@hydrogel hybrid nanogels by polymerizing a hydrogel
shell around the AuNPs that was composed of acid degradable linkers, ionic monomers, and tumor-targeting moieties. Once engulfed by the tumor cells, the polymer portion of the AuNP@hydrogel nanogel could be degraded rapidly in acidic endosomes, leading to the release of pep-AuNPs into the cytoplasm, where caspase-3/7 could cleave the Cy5-labelled peptide, thus freeing Cy5 from AuNPs and increasing fluorescence. The caspase-3/7 activity can, therefore, be related to the intensity of fluorescence. In this approach, the hydrogel shell provided a suitable matrix for AuNPs immobilization, which greatly increased the stability and delivery efficiency by preventing protein corona formation around AuNPs. Overall, this method presented new opportunities for metallic nanoparticle-embedded nanogel based systems for in vivo bio-sensing/imaging applications.

Carbon dots (CDs), which are small carbon nanoparticles possessing fluorescent properties, have many attractive characteristics, such as excellent chemical robustness and inertness, good biocompatibility, environmentally-friendliness, tunable fluorescent properties, as well as simple synthetic procedures [67,68]. Therefore, they have been extensively investigated for building optical sensing platforms, especially for constructing biosensors [63,68]. The combination of CDs and polymeric micro/nanogels can further...
provide some unique opportunities in these areas, as shown by the study from Li et al [63]. In this example, a temperature sensitive carbon dots/SiO$_2$ /molecularly imprinted polymer (CDs/SiO$_2$/MIP) system for cytochrome c (cyt c) sensing was developed. In their work, CDs acted as the fluorescence source; the silanized CDs were the anchors for further molecular imprinting polymerization using NIPAm and MAA as the functional monomers, and N- and C-terminal nonapeptides of cyt c as the templates. The hybrid CDs/SiO$_2$/MIP nanogel exhibited selective cyt c capture, which led to fluorescence quenching of CDs due to the FRET mechanism resulting from the interaction between cyt c and the recognition cavities. The imprinted cavities in the polymer were tested for the selective binding of cyt c by competitive binding experiments with other proteins, lysozyme (Lyz) and trypsin (Try). This assay ultimately showed that although Lyz and Try have similar molecular weight to cyt c, they did not match the binding

Figure 7. Detection of cyt c using the CDs/SiO$_2$/MIP nanogels. (a) Schematic illustration of nanogel synthesis and reversible binding mechanism. (b) Temperature-response of the fluorescence signal of the nanogel upon exposure to cyt c. (c) Fluorescence emission spectra of nanogels with different concentrations of cyt c added, inset was the plot of ($F_0/F$)-1 against the concentration of cyt c, showing a linear relationship. Reprinted (adapted) with permission from ref [63]. Copyright 2016, Elsevier.
sites and therefore did not effectively quench fluorescence. As demonstrated by the authors (Figure 7), their sensor was able to detect cyt c in the range of 0.1 to 40 μM with a limit of detection of 89 nM. The selection of NIPAm and MAA as functional monomer units to synthesize the polymeric nanogel network enabled unique advantages from this system. First, the nonapeptide template could be pre-assembled with NIPAm and MAA via double hydrogen bonding effects, thus increasing overall template incorporation efficiency and further target recognition ability/sensitivity. Second, the temperature responsive pNIPAm polymer shell allowed reversible swelling/deswelling of the nanogel in response to temperature, which could translate into a temperature-reversible presentation of the template as well as temperature-reversible binding of the target molecule, making the fluorescent signal respond to temperature as well. In summary, this novel CDs/MIP nanogel sensor broadened the horizons of using CDs and MIP for optical protein sensing applications.

**Conclusion and perspectives**

As outlined above, the chemical functionality of micro/nanogels can be tailored to achieve responsivity triggered by specific stimuli. Chromophores and luminophores can be attached to the polymeric chains of such micro/nanogels, which allow them to be used for sensing by monitoring changes in electromagnetic field phenomena. While analytes can react directly with fluorophores attached to the micro/nanogels to produce changes in fluorescence, changes in the micro/nanogel solvation state as a result of their interaction with analytes can also produce changes in fluorescence intensity via FRET. Similar to micro/nanogels using either chromophores or luminophores, nanomaterials were immobilized in micro/nanogels to generate specific fluorescent characteristics. In addition, stimuli-responsive micro/nanogels have been employed as elements in photonic devices. The stimuli-responsive behaviors of micro/nanogels can be converted into optical property changes of the photonic material, and likewise employed for sensing. Therefore, the devices bridge the relation between molecular responses and detectable signals.

Although a lot of milestones have been achieved in the field of micro/nanogel research, there are still plenty of interesting areas that need exploration. For example, the colorimetric characteristic of the micro/nanogel-based photonic devices provides a variety of opportunities as wearable sensors. The users could know the concentration of metabolites in body fluids by visually observing color changes and further obtain information about their health. This kind of device can also be used to detect bacteria and other organisms in the wound healing process. This will be beneficial to prevent the occurrence of serious infections. Of course, modification of the
technology to detect emerging viruses is of utmost importance. On the other hand, there are still various applications left to study in regard to new stimuli responsive micro/nanogels, such as radiation-responsive microgels. The detection of X/γ-ray in clinical medicine, nuclear power plants, and war zones is still a great challenge today. The radiation-responsive micro/nanogels would find important applications, resolve some global issues, and generate new theory and knowledge, all throughout the research. The hope for this paper is to acquaint readers with new achievements in the field of micro/nanogels and to inspire even more innovative research.

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