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INVITED REVIEW

# Nanocomposite polymer hydrogels

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**Abstract** The technological need for new and better soft materials as well as the drive for new knowledge and fundamental understanding has led to significant advances in the field of nanocomposite gels. A variety of complex gel structures with unique chemical, physical, and biological properties have been engineered or discovered at the nanoscale. The possibility to form self-assembled and supramolecular morphologies makes organic polymers and inorganic nanoparticles desirable building blocks for the design of water based gels. In this review, we highlight the most recent (2004–2008) accomplishments and trends in the field of nanocomposite polymer hydrogels with a focus on creative approaches to generating structures, properties, and function within mostly biotechnological applications. We examine the impact of published work and conclude with an outline on future directions and challenges that come with the design and engineering of new nanocomposite gels.

**Keywords** Hydrogel · Nanocomposite · Nanoparticle · Polymer · Silicate · Metal nanoparticle

## Introduction

Recent advances in the chemical, physical, and biological fields combined with rising needs in the biomedical and pharmaceutical sectors have led to new developments in nanocomposite hydrogels for many diverse applications. Novel polymer chemistries and formulations as well as fabrication and processing techniques are supported by improved instrumentation that can measure and manipulate matter at the nanoscale level [1]. Theoretical work nicely guides and complements but, at times, contradicts experimental research forcing scientists to collaborate at interdisciplinary boundaries. Nano- and biotechnologies offer opportunities to develop complex and optimized soft materials with synergistic properties. The possibilities to control chemical and physical properties via the design of 3D gel structures provide a powerful strategy for incorporation of versatility into engineering gels from the nanometer scale.

The scope of this review is to delineate the structures and properties of nanocomposite hydrogels made of predominantly synthetic materials. The majority of synthetic hydrogel nanocomposite publications focus on systems utilizing poly(ethylene oxide), poly(acryl amide), or poly(vinyl alcohol) as the polymer. Therefore, hydrogel nanocomposites containing these polymers will receive the majority of our attention in this review. In addition, we will also discuss polymer–metal, polymer–magnetic, and natural polymer nanocomposite hydrogels. Patent literature is not included in this search. Since nanocomposite polymer hydrogels are sometimes difficult to classify when compared to nanocomposite gels, we use here one of the more simplified definitions according to Weiss and Terech, "…if it looks like 'Jell-O', it must be a gel!" [2] Many definitions for gels are available, and researchers do not always agree on what is a hydrogel. Therefore, we will review literature based on nanocomposite hydrogels and gels made from a variety of polymers and inorganic nanoparticles of different sizes. We will not make any distinction between a gel and hydrogel. We will instead use the two terms as they appear in publications.

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In general, nanocomposite polymer hydrogels may be defined as cross-linked polymer networks swollen with water in the presence of nanoparticles or nanostructures. The polymer is cross-linked to form a network via chemical or physical interactions (Fig. 1). The chemical cross-linking is permanent due to covalent bonds. The physical interactions are non-covalent in nature and often a result of hydrogen bonding, hydrophobic, and ionic interactions. The cross-linked polymer networks are capable of reversible volume change in response to external stimuli such as composition [due to (de)swelling], temperature, and pH. The presence of nanoparticles can be used to either cross-link the hydrogel, to adsorb or attach to polymer chains, or to add new properties to the hydrogel by simply being entrapped within the hydrogel network. Nanoparticles add unique physical properties to polymer hydrogels such as responsiveness to mechanical, optical, thermal, barrier, sound, magnetic, electric stimulation, etc. These unique properties lead to applications in the electronics, optics, sensors, actuators and microfluidics sectors, as well as catalysis, separation devices, drug delivery, and many other biotechnological areas.

The combination and formulation of synthetic and natural polymers with nanoparticles and biomolecules

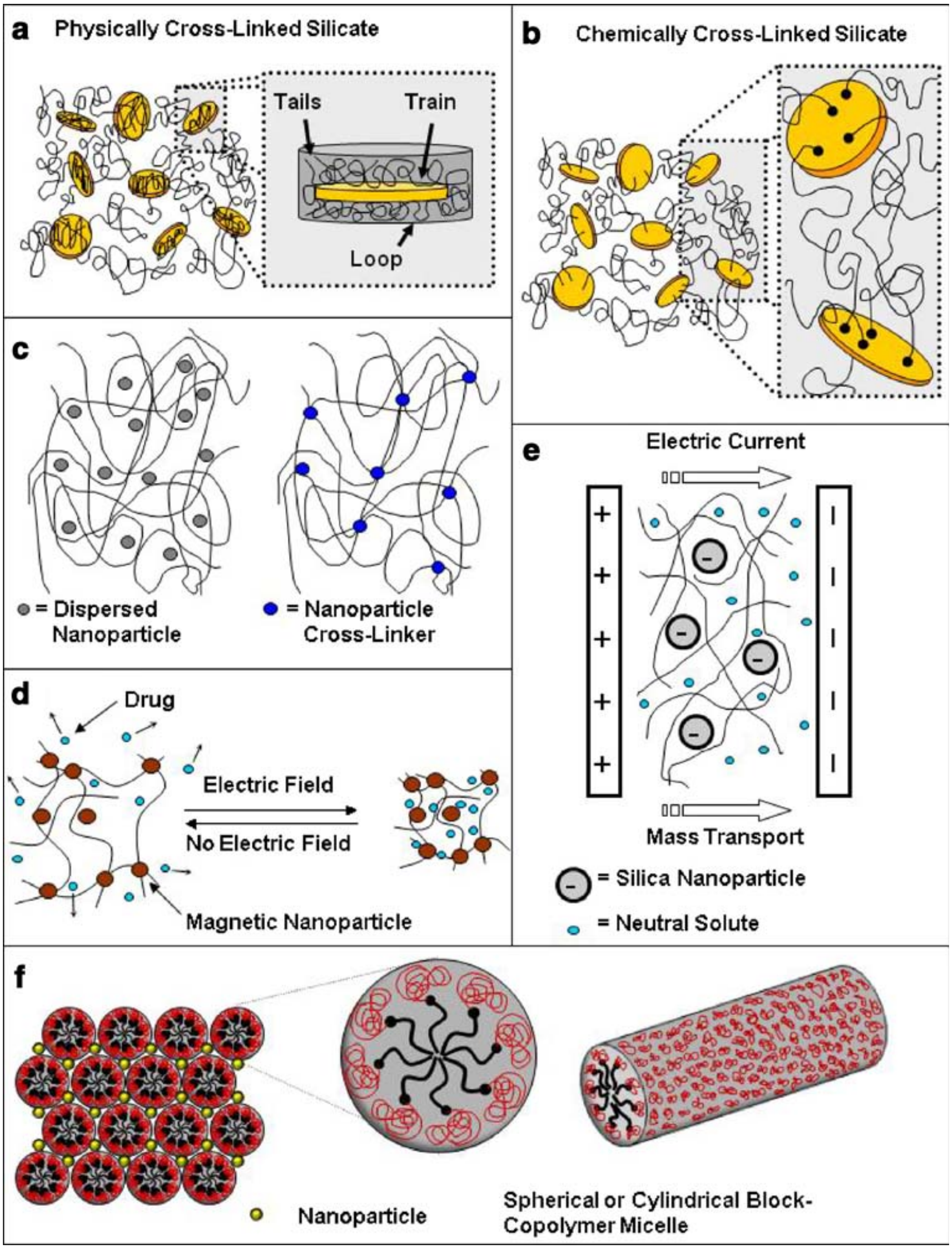

**Fig. 1** **a** PEO chains absorb and desorb on the surface of Laponite particles. *Inset*: Loops and trains are sites of physical interaction between PEO and Laponite forming a PEO shell (*shaded region*) around the Laponite core (disc). PEO tails bridge between multiple Laponite particles, allowing Laponite to function as a physical cross-linking agent [4, 5]. **b** Polymers (PAM and PNIPAM) are chemically bonded to the surface of Laponite during the radical polymerization process [28, 29]. **c** Inclusion of metal nanoparticles (i.e., Ag, Au) dispersed within polymer hydrogels can improve electrical conductance and anti-microbial properties [23, 47]. In addition to being dispersed, nanoparticles can also function as cross-linking (physical and chemical) agents [4, 5, 28, 29, 74]. **d** Polymer–magnetic nanocomposites, with particles in the polymer matrix (dispersed within and/or cross-linking polymer chains), can be used for the remote release of drugs [27, 57]. **e** Negatively charged silica nanoparticles are immobilized within a PAM matrix. An applied electric field causes electro-osmotic flow of silica particles, and viscous drag within the fluid results in the mass transport of neutral solutes (drugs, proteins, etc.) smaller than the gel pore size [42]. **f** Templated block-copolymer gel with nanoparticles residing in the interstitial space between neighboring micelles [18, 19]

synergistically allows combining advantageous chemical, physical, and biological properties to produce nanocomposite hydrogels that support the repair and regeneration of human tissues and body functions. We will review the most recent examples of nanocomposite hydrogels for biomaterials and tissue engineering and focus on recent developments besides what is covered by other reviews [3]. Finally, we conclude with a brief outline on perspectives for the future and challenges that drive the development for novel nanocomposite polymer hydrogels.

## Polymer/silicate-based nanocomposite gels

Incorporating silicate nanoparticles adds mechanical strength to hydrogel materials. However, charged nanoparticles, such as silicates, may exfoliate easily in water due to the colloidal interactions that stabilize the resulting gel. Nanoparticles that are neither charged nor stabilized by salt or polymer usually aggregate. Such aggregates strongly affect the morphological structure of a nanocomposite hydrogel and its mechanical properties. For preparing stable hydrogels, the nanoparticles need to be well dispersed and the resulting large-scale structures need to be controlled. With this in mind, silicates are predominately added to poly(ethylene oxide) and poly(acryl amide) matrices to function as cross-linking agents and to improve network strength.

### Poly(ethylene oxide)–silicate nanocomposites

Published work on gels made of poly(ethylene oxide) (PEO) and silicate nanoparticles goes back more than a decade; thus, research highlighted in this review is based on the exploratory research and materials development done in the past. Since then, nanocomposite hydrogels from Laponite (=silicate nanoplatelets, 30-nm diameter, 1-nm thickness) and PEO have been used as model systems with which to study polymer–nanoparticle interactions and shear orientation on a more fundamental level. Silicate nanoplatelets (Laponite) are synthetic and plate-like poly-ions that uniformly disperse in water and act as multifunctional cross-links to the PEO. The cross-linking is reversible because the polymer readily adsorbs and desorbs from the nanoparticle surfaces. While the polymer properties have been studied in detail, the exact interactions between the PEO and silicate are not clear. However, most scientists agree that hydrogen bonding, ionic, dipole, and other interactions such as polymer entanglements must play a role when cross-linking to the silicate takes place. More quantitative studies by Nelson and Cosgrove [4, 5] suggest that PEO adsorbed onto Laponite particles, forms a compact layer of mostly trains and loops on top of the nanoparticle and large loops around the edge of the particles (Fig. 1a).

The hydrogel structures and viscoelastic properties can be tuned by changing parameters such as composition, pH, temperature, and ionic strength. For example, by varying the Laponite and PEO compositions, one may generate solutions, flowing gels, shake gels, or permanent hydrogels that can be swollen by the addition of water [6–9]. The shear-induced gelation of shake gels is reversible and strongly dependent on the PEO concentration, time, temperature, and molecular weight [6, 7, 10]. According to this published research, the shear deforms the large PEO–Laponite aggregates and exposes fresh surface area for the formation of new polymer bridges, which rapidly form a network that spans the entire solution and forms a gel. When the shaking stops, thermal fluctuations are sufficient to desorb the polymer from the nanoparticle, and the hydrogel relaxes back to a fluid after some time. The applied shear is not high enough to overcome randomizing effects caused by the polymer and nanoparticle relaxations.

The kinetics of gel formation in Laponite–PEO dispersions of varying polymer molecular weight ($M_w$) was studied using rheology [8]. The mechanisms of gel formation were found to be time-dependent. Other work by the same group showed a reentrant behavior from soft solid to liquid back to soft solid as the PEO molecular weight is increased [11]. A paper published by Daga and Wagner [12] presented the viscoelastic and relaxation behavior of Laponite–poly(ethylene oxide) gels over a range of concentrations. Time–temperature and time–concentration superposition were applied to generate rheological master curves. The addition of Laponite to a concentrated polymer solution increased the relaxation time but decreased the elastic modulus, which was attributed to the polymer adsorption and bridging.

At high polymer and Laponite concentrations, Loizou et al. [9] reported strong gels with gum-like consistency. The polymer -coated silicate nanoplatelets were found to be dynamically tethered together in loose bundles that form fractal-like structures with “pores” into the micrometer regime. A skeleton-like structure on the nanometer and micrometer length scale would account for the lack of flow in a gel containing mass fractions of 95% water. The cross-linking is physical (not covalent) owing to hydrogen bonding, dipole, ionic, and other interactions that attach the polymer chains to the nanoparticles. The cross-linking of hydrogels is reversible because under deformation, the polymer chains may attach to and detach from the nanoparticles. The hydrogels usually shear thin, a property that makes some of them injectable via syringe. After cessation of shear, the macrostructure and rigidity of the hydrogel recovers completely within seconds, suggesting self-healing properties [13].

The shear-induced micron-sized structures observed by Loizou et al. are consistent with previous studies on similar systems which observed transient micron-scale heterogeneities [14] that develop during shear and disappear upon cessation of shear. While in this case shear may induce the development of new structure, it is also possible that already existing structures may disappear. For example, studies by de Bryun et al. [15]. show the presence of micron-sized PEO–Laponite aggregates in hydrogels break up and disappear above a critical shear rate.

To summarize, the reviewed work collectively indicates that the interactions between PEO and silicate (Laponite) nanoparticles are strongly influenced by shear which contributes to the complex behavior of these hydrogels. The soft, rubbery consistency and the flexibility in varying the mechanical properties make these hydrogels potential candidates for many technical applications, among them biomedical technologies. However, few applications have been reported despite the great interest in basic research. In one of these applications, Takahashi et al. [16] has shown that a modified PEO–Laponite system can be developed into a drug delivery system at physiological conditions. A broader variety of applications is mentioned for colloidal dispersions (attractive gels) made from nanoparticulate bentonites (natural layered silicate) and PEO polymer. Sol–gel phase diagrams in water clearly show gel regions as a function of composition, although it is not clear if these gels have 3D stable structures as required by hydrogels. The yield stress of the gels and their sol–gel transitions are useful properties in technical applications such as oil well drilling, antifriction agents, additives for concrete, mortar and emulsions, shear thickening paints, cosmetics, and pharmaceuticals [17].

More precise spatial and orientational positioning of nanoparticles within a hydrogel matrix can be achieved by the use of block copolymers instead of homopolymer hydrogels. The block copolymer gel imposes its liquid crystalline order on the nanoparticles which do not self-assemble on their own [18]. For example, nanocomposite hydrogels based on PEO–polypropylene oxide (PPO)–PEO block copolymers and spherical silicate nanoparticles (7 nm) have been investigated for the formation of templated nanoparticle arrays [19]. The isotropic to liquid crystalline phase transitions in Pluronic type PEO–PPO–PEO hydrogels can be used to disperse and order silica nanoparticles on a nanometer length scale (Fig. 1f) [18]. Shear is used to align the nanocomposite hydrogel towards macroscopic crystal domains. Cylindrical micellar templates as reported by Pozzo and Walker [19] can then be used to form linear nanoparticle arrays which may allow for the future fabrication of linear waveguides. Similar orientational work on PEO–PPO–PEO block copolymer cross-linked with Laponite indicates that the PPO segments preferentially adsorb onto the Laponite surface, leaving the PEO segments dangling away from the nanoparticle [20]. Overall, block copolymer nanocomposite hydrogels can be designed to have sophisticated new properties via self-assembly that the homopolymer counterparts do not have.

## Poly(acryl amide)– and poly(vinyl alcohol)–silicate nanocomposites

The reviewed research on silicate–PEO hydrogels parallels that of poly(acryl amide) (PAM)-based gels such as poly(*N*-isopropyl acryl amide) (PNIPAM) in many aspects. The similarities and differences between silicate cross-linked PEOs and PAMs lie in the polymer chemistry that controls structures and properties. Hydrogels based on PAMs may show sensitivity towards external stimuli such as pH, light, temperature, solvent, pressure, mechanic, electric, and magnetic fields [21–27].

The chemical cross-linking of PAM-based polymers (e.g., PNIPAM or PAM) with silicate nanoparticles (Laponite, montmorillonite, etc.) leads to nanocomposite hydrogels with a range of properties that have attracted many researchers (Fig. 1b). Specifically, the thermosensitive coil to globule transition and the lower critical solution temperature of PAM polymers are of interest. The synthesis of hydrogels often requires the polymerization to be initiated from the silicate, followed by the formation of brush-like silicate surfaces. While the brush polymers grow longer, they interconnect several silicate nanoparticles and form a cross-linked polymer network [28, 29]. Haraguchi and Li [30, 31] compared the structure of organically cross-linked (OR) gels with Laponite cross-linked PNIPAM nanocomposite (NC) gels. This group discovered that the number of cross-linking units per space is 700 times higher for the OR gels compared to the NC hydrogels. OR gels with a broad distribution of polymer chain lengths between the many cross-linking points build up high localized stresses under deformation and fracture easily. However, NC gels that have similar polymer chain lengths and a more homogeneous distribution of Laponite cross-linkers avoid the localization of stress during deformation and exhibit extraordinary mechanical properties. The PAM polymers chains are more flexible than the PNIPAM polymer, which leads to differences in elastic recovery, hysteresis, tensile strength, and elongation [28]. Spatial homogeneity can be measured via optical transparency or scattering techniques. Nie et al. [32, 33] studied network structure, degree of spatial inhomogeneity, and chain dynamics. It was determined that the thermal fluctuations of nanoparticles are largely suppressed by the network formation and that chain dynamics are more or less independent of the cross-linking agent. Overall, these studies suggest that the effective functionality of the Laponite cross-linkers is around 50 and that this high functionality as well as large correlation lengths generate the large-scale structures that lead to outstanding mechanical properties [30–34].

Mu and Zheng [35] prepared PNIPAM hydrogels that were cross-linked with hydrophobic polyhedral oligomeric silsesquioxane (POSS). These hydrogels exhibited marked improvement in the temperature swelling/de-swelling kinetics. In addition, the POSS cross-linkers increased the mechanical strength of the hydrogels, which in turn allowed for an increase in the number of swelling/de-swelling cycles without noticeable degradation of the hydrogel. The swelling/de-swelling of the PNIPAM–POSS hydrogel is much faster (minutes versus hours) than PNIPAM–Laponite hydrogels, but this improvement is especially true at higher cross-linker concentrations [31, 35].

A recent paper compares the swelling behavior of PAM hydrogels cross-linked with different silicates (attapulgite, kaolinite, mica, vermiculite, and montmorillonite). The authors report that the type of silicate used to cross-link PAM affects the swelling properties and thermal stability of the hydrogel as well as the polymerization reaction mechanism. Therefore, the cross-linker chosen should be based on the application of the hydrogel. For example, a montmorillonite cross-linker should be chosen for applications in which a fast swelling rate is needed, but a mica cross-linker should be chosen if the hydrogel needs to swell/de-swell multiple times [36]. Another recent paper, by Ziesmer and Stock [37], mentions the preparation of PNIAPM–zeolite and poly(vinylpyridine)–zeolite nanocomposite hydrogels. These authors report the synthesis of core–shell structures with the use of a microporous zeolite core material which are temperature (PNIAPM–zeolite) and pH [poly(vinylpyridine)–zeolite] responsive, having strong potential in controlled release and separation applications.

Besides PAMs, other polymers such as poly(vinyl alcohol) (PVA) have been used for making nanocomposite hydrogels. Adding montmorillonite nanoparticles to PVA can increase the mechanical strength of a hydrogel so that the hydrogel can be used in high shear applications [38]. The addition of surfactant to PVA is usually applied to change the polymer interactions with the silicate, as small amounts of surfactant increase the network strength of the hydrogel by strengthening the interaction between PVA and silicate. However, a further increase of surfactant concentration disrupts the PVA–silicate binding, which in turn disrupts the hydrogel network into a viscous solution [39]. Paranhos et al. [40] report that the amount of montmorillonite contained within a PVA–silicate hydrogel (up to 5%) increases PVA crystallite size, decreases the pore size within the hydrogel, and decreases the mobility of PVA chains. However, addition of a second polymer (a sulfonated polyester) has an opposite effect on PVA, giving researchers better control of crystallinity in PVA–montmorillonite hydrogels [41].

Prospects for applications are multifold and most recent ones are in the sensors, actuators, and general biomedical sector. For example, Haraguchi et al. [24] have used the sensitivity towards external stimuli to develop silicate cross-linked PAM and PNIPAM gels into smart drug delivery vehicles. The in vitro and in vivo biocompatibility, the antithrombogenicity, as well as the thermosensitivity of these materials suggest applications as biomaterials for contact lenses or implants. In addition, the mechanical toughness is useful for development of elastic biomaterials such as sutures and artificial tendons.

In another example, Matos et al. [42] have used PAM-based hydrogels doped with spherical silicate nanoparticles (7–15 nm) to improve the performance of biosensors by electro-osmotically enhancing the mass transfer of solutes through the gel. While electrophoresis does not drive neutral molecules and thus cannot be used for mass transfer enhancement, the internal pumping method developed by Matos et al. [42] generates electro-osmotic flow around charged silicate nanoparticles surfaces which in return allows mass transfer of neutral molecules/solutes though hydrogels (Fig. 1e). A quantitative theoretical interpretation of the experimental data by Matos et al. is presented by Hill [43]. Hill uses a mathematical model for the electro-osmotically enhanced tracer flux combined with an electrokinetic model to determine the electro-osmotic pumping velocity from flux enhancements [43]. After considering several approaches to compare theory and experiments, he concludes that the macroscale properties are linked to the microstructural characteristics, which need to be included into future theoretical approaches.

## Polymer–metal nanoparticle hydrogels

Hybrid materials can be obtained by combining metal-based nanoparticles such as gold and silver with polymer hydrogels. There is little effect on the mechanical properties of the resulting nanocomposite hydrogels by the incorporation of metal nanoparticles as long as the interactions between polymer and nanoparticles are weak. In this case, phase transition, thermosensitivity, and viscoelasticity of the polymer gel remain unchanged, and the properties of the nanoparticle such as improved electrical conductivity, response to optical stimuli, improved antimicrobial properties, etc. are added to the gel.

Stronger polymer–nanoparticle interactions that are induced, e.g., by the attachment of gold reactive thiol groups to the PNIPAM hydrogel, may change thermosensitivity and swelling behavior [44]. This way, gold nanoparticles form covalent bonds to PNIPAM (Fig. 1c). The resulting nanocomposite gels then have electrical properties that may change by two orders of magnitude with temperature. This change in electrical conductivity is due to the change in the average interparticle distance which is dependent on the coil to globule transition of the PNIPAM gel [23]. Another application of gold nanoparticle hydrogels describes how the spatial coupling of the nanoparticles is dependent on the stimuli induced swelling/de-swelling of the poly(2-vinyl pyridine) polymer. This pH-dependent process changes the localized surface plasmon resonance, allowing the material to analyze pH by measuring the change of the UV–vis spectrum of the hydrogel. The authors report a significant improvement in sensitivity and processing conditions compared to other technologies [45].

Silver nanoparticles (3–8 nm) add electronic and antibacterial properties to a variety of polymer hydrogels [46, 47]. Usually, carboxylic acid groups can be used as a temporary anchoring agent for attaching silver cations to polymer hydrogels, and the silver is reduced to form nanoparticles with sodium borohydride [48]. This method of preparation depends on the number of functional groups present to stabilize the silver ions, but the nanoparticles are dispersed within the hydrogel matrix. Others have prepared immobilized silver nanoparticles within PAM hydrogels with improved electrical properties [49], but the immobilized silver particles may not prove to be antimicrobial. However, Murthy et al. [50] were able to stabilize the silver ions without the presence of ionic functional groups in a semi-interpenetrating network composed of PAM-poly(vinyl pyrrolidine) and prepare dispersed silver nanoparticles with a higher yield. Another group was able to prepare silver nanoparticles in which the silver ions were stabilized by carboxylic acid and amine groups within a fatty acid–amine hydrogel. Interestingly, the silver nanoparticles were primarily imbedded within the self-assembled long fibers of the hydrogel matrix, providing a method to order metallic nanoparticle regions within a hydrogel system [51].

When 2-hydroxyethyl methacrylate (HEMA)–poly(ethylene glycol) methyl ether methacrylate (PEGMA)–methacrylic acid (MAA) is used as the polymer, the resulting hydrogel has pH-switchable electronic properties. The pH responsiveness is related to the deprotonation of carboxylic acid groups that cause hydrogel swelling [48]. The electronic properties of these gels could lead to smart materials used in biosensors and drug delivery applications as well as drug carriers for biomolecules such as enzymes. Lu et al. [52] reported multicomponent hydrogels made from polymer particles that are decorated with polymer brushes (nanotrees) and cross-linked within a poly(vinyl alcohol) matrix. Additional silver nanoparticles (35 nm) are generated on the surfaces of the brush particles or within the PVA matrix. The resulting hydrogels have catalytic activity that is retained over several months.

In addition to gold and silver, other nanoparticles such as iron, cobalt, nickel, copper as well as metal alloys, salts, and metal-derived quantum dots (2–100 nm) can be mixed with or synthesized within a hydrogel matrix [53, 54]. The applications of these hydrogels are found in catalysis, sensors, actuators, and microfluidic devices as well as separation technology. However, only nontoxic biomaterials will find use in the pharmaceutical and medical fields.

## Polymer–magnetic nanoparticle hydrogels

The properties of magnetic nanocomposite hydrogels (ferrogels) have received considerable attention, and a good review focusing on this topic is available [55]. While ferrogels can be made using other solvents than water (e.g., oil), here, we focus on reviewing aqueous gels only. The coupling of magnetoresponsive and thermosensitive properties allows for the development of nanocomposite hydrogels that one may call smart. Similar to the synthesis of other nanocomposite hydrogels, the nanoparticles (10–500 nm) can be either dispersed or chemically attached to the polymer network, but the magnetic nanoparticles are generally synthesized in situ with the polymer matrix to prevent agglomeration [56]. Analysis of the magnetic relaxation behavior of dispersed magnetic nanoparticles allows for distinguishing between physically entrapped and mobile nanoparticles. The polymers used to form the hydrogel matrix are often PAM-based such as PNIPAM [27] or biopolymers such as gelatin and starch gels [56].

Gels containing magnetic nanoparticles show size dependence of properties that are very different from magnetorheological fluids containing micron-sized particles. Nanoparticles used are made of iron, cobalt, nickel, or iron oxides. Nanoparticle rotations or alignments in response to a high-frequency magnetic field allow magnetic nanoparticles to heat up the surrounding hydrogel matrix in which they are trapped. Such remote heating could be used for inducing noninvasive focused hyperthermia, for controlled drug release, and for triggering thermosensitive changes in hydrogel volume or shape (Fig. 1d) [27, 57]. Magnetic hydrogels thus offer ways to selectively target, detect, and potentially treat cancer tissue via magnetic resonance imaging and inductive heating [58].

Besides the biomedical applications mentioned above, magnetic hydrogels are potentially attractive to the development of other technologies including nanomotors, sensors, robot-like soft actuators [59], and a variety of separation devices [55, 59].

Finally, it is worth mentioning that macroscopic hydrogel matrixes are advantageous materials for nanoparticle synthesis because they prevent aggregation and diffusion of the nanoparticles during synthesis. Thus, nanocomposite hydrogels are often found to be just templates for growing inorganic nanoparticles, and the authors are often more interested in the nanoparticle itself than in the nanocomposite hydrogel [60].

## Nanocomposite hydrogels with natural polymers

In addition to reviewing synthetic gels, we include “manmade gels” from natural polymers and nanoparticles. While biological hydrogels seem to have near-infinite structural complexity (extracellular matrix, cells), gels from natural polymers with no tertiary structure often have similar chemical and physical properties, most of which can be related to synthetic hydrogels [61].

Natural polymers (starch, chitosan, alginate, etc.) are increasingly reported as polymers used in nanocomposite hydrogels. This is predominately due to advantageous properties of natural polymers (e.g., biocompatibility, biodegradability, low cost). A common technique used in the preparation of natural polymer nanocomposites is the chemical modification of the polymer to improve the polymer–nanoparticle interaction and form a mechanically stable hydrogel. However, the chemical modification of biopolymers (the grafting of functional groups or synthetic polymer onto the polymer) may change the biocompatibility of the natural polymer due to the incomplete removal of toxic chemicals during the synthetic modification, which is a common reason for using unmodified natural polymers. One method to induce gelation of natural polymers, proposed by Shchipunov et al. [62], involves mineralization of the polymer (chitosan, guar gum, carboxymethylcellulose, β-cyclodextrin, etc.) with silica. In this work, water-soluble tetrakis(2-hydroxy ethyl) orthosilicate (THEOS) was dissolved along with the polymer. THEOS hydrolyzes in situ to produce silica nanoparticles which cross-link the polymer. The authors report that this procedure enables the gelation of a diverse group of otherwise non-gelable polysaccharides containing cationic, anionic, linear, or branched regions. A more recent report describes the gelation of hydroxypropyl guar gum with THEOS and the release kinetics of a model drug loaded within the hydrogel matrix [63].

Stimuli-responsive nanocomposite hydrogels containing natural polymers, like their synthetic polymer counterparts, have primarily been studied for their response to changes in pH and temperature. Ma et al. [64] found that carboxymethyl chitosan–PNIPAM interpenetrating networks cross-linked with Laponite undergo similar phase transitions at ~33 °C as PNIPAM–silicate hydrogels. However, the carboxymethyl chitosan-containing hydrogel could absorb more water than the nanocomposite consisting of PNIPAM–silicate when the pH was less than ~2.5 or greater than ~4. The authors attributed this increase in swelling to the hydrophilicity of carboxymethyl chitosan. In addition, the chitosan-containing composite had a larger volume change with pH due to the amphoteric functional groups ($–NH_2$ and $–CH_2COOH$) present in the chitosan derivative. The same group found a similar trend with carboxymethylcellulose–PNIPAM semi-interpenetrating networks that were cross-linked with Laponite. In this case, the cellulose only contained one ionizable functional group and exhibited a peak in swelling ratio when the carboxylic acid groups are deprotonated (pH ~4.6) due to electrostatic repulsions. Below this pH, hydrogen bonds form and reduce the swelling capacity, while above this pH, sodium counterions screen the electrostatic repulsions [65].

## Microgels from polymer–nanoparticle hydrogels

A large body of literature and some recent reviews [66–68] cover the synthesis, characterization, and applications of polymer microgels containing inorganic and magnetic nanoparticles. The microgels are often composed of spherical nano- or micron-sized particles made of hydrogels stuffed with inorganic nanoparticles. The terms microgels and nanogels are often found to be used for the same type of materials, but the definitions of these terms are not always clear when compared to macroscopic hydrogels containing nanoparticles. According to Pich and Adler [66], microgels are described as porous cross-linked polymeric particles that change their properties in response to surrounding conditions. The review by Pich and Adler [66], as well as that by Dimitrov et al. [67], nicely review and highlight developments in magnetic and nanoparticle-based microgels within the last 20 years. A complementary review article by Das et al. [68] describes microgels as “old materials with new applications.” Such new applications include the use of microgels as microreactors for templated synthesis of inorganic nanoparticles. The properties of optically active materials including lenses and photonic crystals are discussed and new microgel applications in drug delivery are covered [68]. Despite the large amount of literature summarized in these reviews, the field encompassing microgels/nanogels and nanoparticles is quickly growing and cannot be given the necessary attention in this review. The large amount of research published in 2008 alone deserves to be reviewed and summarized on its own.

Here, we swiftly compare microgels to macroscopic and nanocomposite hydrogels. While not focusing on nanocomposites, Nayak and Lyon [69] nicely describe the differences between hydrogels and microgels. They state that hydrogels are macrogels that must be larger than millimeters in size. Microgels are colloidally stable hydrogels of a size that varies from nanometers to micrometers. Although microgels can be described as nano- and microparticles made from a hydrogel, microgels do not necessarily show macroscopic characteristics of hydrogels. Microgels may not have a "macroscopic" yield stress that can easily be measured with conventional rheology. Microgels may not pass the "tube inversion test" (gel supports its own weight upon inversion of a tube containing the gel) [2] because macroscopically seen, microgels might be dispersions and low viscous solutions. However, compared to macroscopic or bulk hydrogels, microgels may respond faster to changes in their environment because their larger interfacial area allows higher exchange rates. For example, Gorelikov et al. [21] were able to prepare PNIPAM microgels containing gold nanorods (6-nm diameter, 12- to 36-nm length) which rapidly underwent a volume change when exposed to near-infrared radiation, giving this material potential in drug delivery applications. When microgels are cross-linked to form macroscopic hydrogels, new properties can be generated. Cho et al. [25] showed that the assembly and cross-linking of PNIPAM microgel particles allows for the formation of novel and highly responsive hydrogel scaffolds that are superior compared to their bulk polymer gel counterparts. A variety of nanoparticles (e.g., silica and magnetic particles) can be structurally locked within these cross-linked microgels for the engineering of stimuli-responsive functional materials. Besides their loading capabilities, nanocomposite- and microgel-based hydrogels maintain their thermosensitivity as well as their fast response kinetics. The quick volume change response of the microgels is not affected by the bulk hydrogel, but the overall bulk gelation time is increased by the inclusion of microgel particles [25, 70, 71].

## Other nanocomposite polymer hydrogels for biomedical applications

As seen above, there are many examples of nanocomposite hydrogels being used as biomaterials in drug delivery, tissue engineering, and general biomedical applications. For a rational design of biocompatible and nanocomposite hydrogels, the structure and properties of the hydrogels must be considered because the nanoscale morphology of the hydrogel surfaces and interfaces will affect cell adhesion, migration, proliferation, and gene expression.

A large number of investigations lyophilize nanocomposite hydrogels and use the resulting matrix in scaffolding applications, particularly bone tissue engineering [72, 73]. Because these investigations use the scaffolding derived from hydrogels, rather than pure nanocomposite hydrogels, reports on dried scaffolds will not be included in this review. Instead, we address the development of predominantly injectable hydrogels scaffolds with nanocomposite structure. A study by Leeuwenburgh et al. [74] involved the functionalization of polymer hydrogels with finely dispersed calcium phosphate nanocrystals for bone repair. Homogeneous hydrogels were fabricated by synthesizing calcium phosphate nanocrystals directly inside a poly(ethylene glycol)fumarate hydrogel. The resulting nanocomposite hydrogel was found to have physical cross-linking between the nanocrystals and carboxylate endgroups of the polymer, which in return reduced the swelling behavior.

Applications of nanocomposite hydrogels for tissue engineering usually depend on the combination of functional properties that are engineered into the nanocomposite hydrogels to make these materials more versatile [75]. For example, Hou et al. [26] prepared thermoresponsive hydrogels from PNIPAM and polysiloxane nanoparticles (approximately 100–500 nm) to modulate cell adhesion. The transition temperature of this nanocomposite hydrogel remains constant (at ~33 °C) when increasing the nanoparticle concentration, but the mechanical strength and cell adhesion increases. Similar to pure PNIPAM, the polysiloxane-containing nanocomposite hydrogel allows cell attachment at 37 °C, but cells detach from its surface at lower temperatures such as 20 °C. This effect originates in the transition of the polymer from collapsed globule to extended coil formation, which causes temperature-dependent hydrophobic interactions. The hydrogel is easily photo-patterned and can be used as implanted sensor membrane or as an anti-fouling coating for biomaterials used in vivo. Most importantly, the hydrogels allow for cell sheet engineering without the need for proteolytic enzymes and chelating agents to remove the sheet of cells from the hydrogel surface. A similar cell detachment phenomenon was also reported in PNIPAM–Laponite hydrogels [24].

Creative approaches incorporate biomolecules into magnetic nanoparticle (5–10 nm) gels for chemotherapeutic loading and for tumor-associated biomolecular binding. For example, Sunderland et al. [58] reported that their hydrogels, so-called MagNaGels's (TM), maintain good magnetic susceptibility and "acceptable" biocompatibility when tested in vivo. However, these gels turn out to be microgels rather than hydrogels.

Finally, nanocomposite polymer hydrogels with bentonite have shown promising potential in drug delivery applications. Lee and Chen [76] describe the feasibility to deliver a variety of model drugs from an acrylic acid-poly (ethylene glycol) methyl ether acrylate hydrogel containing silicate nanoparticles (bentonite). This group found that the elution kinetics are strongly dependent on the interactions between the surface charges of the nanoparticle and the ionic charge of the drug. Ionic attractions between the silicate and drug result in slower release rates, while repulsive interactions between the two increase the rate of drug elution. Takahashi et al. [16] further describe the ability of a PEG–Laponite nanocomposite system to deliver an uncharged hydrophobic drug pyrene. While not focusing on nanocomposite hydrogels, Lynch et al. [77] describe the simultaneous ability to elute multiple model drugs with independently controllable release kinetics from drug loaded "plum pudding" microgels imbedded within a bulk gel. In addition, the authors note that the diffusion of the model drugs is due to the bulk hydrogel and not due to microgels within the material [78]. Others have shown the usefulness of PVA–montmorillonite hydrogels in wound dressing applications. Such mechanically strong hydrogels were able to absorb fluid exudate from wound sites in addition to preventing exogenous bacterial infiltration [38].

## Conclusions and perspectives for the future

Nanocomposite polymer hydrogels are new generation materials useful for a wide variety of applications. From stimuli-responsive sensors and actuators to microfluidics, pharmaceutical, and biomedical devices, the potential impact for nanocomposite hydrogels to influence the lives of the general public continues to grow. The large amount of recent reports has explained some of the physics and chemistry behind the unique properties of these hydrogel materials. Responsive hydrogels that change properties and function as response to external stimuli such as artificial muscles are often inspired by natural systems. Desirable properties such as injectability and precise drug delivery that cannot be controlled with certain macroscopic hydrogels are achieved with nanocomposite micro- and nanogels.

Future directions certainly include the rational design of biomedical nanocomposite hydrogels that require not only control of chemical and physical properties but also the consideration of biological variables. While hydrogels can be used to simulate biological tissues, significant challenges arise when it comes to designing mechanically strong gels with long-term biocompatibility and controlled biodegradability.

Reviewed literature suggests that the development of synthetic routes and fabrication technologies for fundamental understanding of nanocomposite hydrogels will continue, but with a greater emphasis on designing sophisticated multi-component and complex materials that can be tailored to very specific applications. Emerging new techniques strongly support the systematic characterization of nanocomposite gels which, in return, drives research forward and impacts the rational design of materials.

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