Review

Hydrogel Nanoparticle as a Functional Coating Layer in Biosensing, Tissue Engineering, and Drug Delivery

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Received: 4 June 2020; Accepted: 6 July 2020; Published: 10 July 2020

Abstract: The development of functional coating materials has resulted in many breakthroughs in the discovery of energy, environmental, and biomedical applications. Responsive polymeric hydrogels are an example of smart coating materials due to their stimuli-responsive characteristics upon changes in their local environment. This review focuses on the introduction of hydrogel nanoparticles and their applications in functional layers as responsive coating materials. Hydrogels are explained by the composition of cross-links and monomers used for preparation. In particular, an important class of responsive hydrogels, that is, nanosized hydrogel particles (nanogels), are described for their synthesis, modification, and application in assembly of functional coating layers. Finally, nanogel functional layers for biological applications will be discussed with recent advances in biosensing, tissue engineering, and drug delivery.

Keywords: responsive hydrogels; hydrogel nanoparticles; nanogels; smart coatings; biosensing layer

1. Introduction

Hydrogels have dual characteristics in the states of matter, making them complicated to define due to their fluidic and solid-like properties. For instance, hydrogels maintain the structural integrity of a solid when removed from their aqueous container. However, hydrogels enable the transport of small molecules through hydrogel networks thanks to their fluid-like properties. Thus, hydrogels could be defined as cross-linked polymeric materials swelling in an aqueous phase [1–4]. In this definition, hydrogels are considered as cross-linked networks with visco-elastic behavior, providing dimensional stability as a soft material. The swelling behavior of hydrogels is also important to characterize, which allows them to absorb thousand times their dry weight in aqueous media [4–6]. Such swelling properties are tunable by cross-links as well as by monomers. This enables them to act on many stimuli through the endothermic/entropy-driven phase transition [3]. The recent development of responsive hydrogels has advanced the property for novel applications in tunable optical elements [7–11], micro-fluidic flow control [12–17], surface patterning [18–20], sensing transducers [21–28], catalysis [29–32], drug delivery [33–52], protein separation [53–56], cellular/tissue engineering [5,57–63], and bio-assays/sensing [2,21,64–75]. Overall, this review aims to introduce hydrogels by composition and synthesis, followed by describing their responsivity and applications in functional coating layers for biosensing, tissue engineering, and drug delivery.

2. Composition and Synthesis of Hydrogels

2.1. Cross-Links in Hydrogels

Cross-links play a key role in maintaining the structural stability of hydrogels as well as the entanglement of hydrophilic chains. Hydrogels are categorized into physically and chemically cross-linked hydrogels [3]. The networks of hydrogels with physical cross-links are coalesced by noncovalent interactions including hydrophobic interactions, ionic interactions, hydrogen bonds, and protein–ligand bonds [1,3,6,76–81]. Physically cross-linked hydrogels can develop reversibly degradable hydrogels, undergoing a transition from a dimensionally stable polymer to a polymer solution. Noncovalent interactions among hydrogel networks, which are relatively weaker than covalent interactions, facilitate their transition behavior between entangled and dissolved states. These hydrogels are favorable for encapsulating proteins, drugs, or cells and then releasing them from the dissolved hydrogels [33,59,82,83].

For hydrogels with chemical cross-links, their networks are covalently formed by polymerizing monomers with cross-linking agents such as *N,N'*-methylene(bisacrylamide) (BIS), providing stronger hydrogel structures than those of physical cross-links [1,3,15]. In this approach, hydrogel properties are also tunable by incorporating diverse functional moieties into the hydrogel backbone network, which allows for the formation of responsive hydrogels responding to various stimuli. For instance, functional moieties could be like those of peptides and small molecules.

2.2. Monomers in Hydrogels

Hydrogels are polymeric materials prepared by the polymerization of monomers and/or cross-linking agents in the presence (or absence) of a surfactant. Thus, the physiochemical properties of the polymeric hydrogels are mainly determined by the monomers used for the polymerization. Based on the type of the monomers used, the hydrogels are enabled to undergo a phase transition in response to external stimuli such as temperature, pH, photon flux, ionic strength, and electric currents [7,10,84–102]. *N*-Isopropylacrylamide (NIPAm) is an extensively used monomer for hydrogel formation due to its temperature-dependent behavior in aqueous solutions, which results in the formation of thermoresponsive poly(*N*-isopropylacrylamide) pNIPAm hydrogel via a number of polymerization methods [92,96,103–109]. Such hydrogels undergo a reversible phase transition at the lower critical solution temperature (LCST) or upper critical solution temperature (UCST) of the polymer as the hydrogel goes from a swollen state to a deswollen state, or vice versa [84,86,96,110,111]. By adding another monomer (i.e., acrylic acid (AAc)) during the polymerization process, the thermoresponsive hydrogels can be equipped with pH responsivity, which allows for the formation of the thermo/pH-responsive poly(*N*-isopropylacrylamide-*co*-acrylic acid) (pNIPAm-*co*-AAc) hydrogels [87,112,113]. A similar approach could be used to make hydrogels attractive for a number of applications as smart materials.

2.3. Synthesis of Hydrogel Nanoparticles

A nanogel is a type of hydrogel particle with submicron size that is able to bring additional properties in comparison to bulk hydrogels. For instance, the response rate of pNIPAm nanogel is faster than that of bulk hydrogels. Such nanogels have been prepared by a number of synthetic protocols including precipitation polymerization, miniemulsion polymerization, and microemulsion polymerization [96,109,114–123]. The temperature-induced precipitation polymerization method for pNIPAm-*co*-AAc nanogel has been widely used due to both the water solubility of the precursor monomers and the reduced solubility when polymerized under the absence of oxygen (O₂) from the reaction mixture (Figure 1). Precipitation polymerization is typically carried out in a three-neck round-bottom flask containing water purged with nitrogen gas. The purge is required to remove any dissolved O₂ from the reaction mixture, as O₂ acts as a free-radical scavenger that prevents the polymerization reaction from occurring. The solution of main monomer NIPAm and the crosslinker

N,N'-methylene(bisacrylamide) (BIS) are stirred and heated above the LCST of the NIPAm. The addition of comonomers into the mixture enables the hydrogels to acquire various functionalities depending on the monomers. Surfactants such as sodium dodecyl sulfate (SDS) and Tween 80 can be used as nanogel stabilizers in these reactions. Note that the modulation of SDS content during a polymerization reaction can be used to control the hydrodynamic radius of the hydrogel.

Figure 1. Common monomers used in the synthesis of thermo/pH-responsive microgels. NIPAm: N-isopropylacrylamide, AAc: acrylic acid, BIS: *N,N'*-methylenebisacrylamide.

The polymerization reaction can be initiated by adding a free-radical initiator such as ammonium persulfate (APS). The addition of APS produces free radical fragments, which enables them to react with monomers and cross-linkers in the solution. Herein, pNIPAm chains are formed homogeneously and then collapsed to form precursor particles when they reach a certain critical chain length. Precursor particles can serve as nuclei for nanogel formation, with a diameter that can be modulated by the amount of surfactant SDS present in the reaction mixture [104,124–126]. For example, a higher SDS concentration results in smaller nanogels until reaching the critical micelle concentration (CMC), while lower SDS concentrations result in larger nanogels. The various stages of nanogel growth during the reaction procedure are illustrated in Figure 2. As discussed previously, numerous comonomers are available that can be added to the reaction mixture to add multiple functionalities to nanogels. Alternatively, polymerized hydrogels can be post-engineered by coupling chemistry, such as carbodiimide reactions, which is widely used to conjugate biological molecules with hydrogels.

Figure 2. Schematic of the various stages of nanogel growth during precipitation polymerization involving pNIPAm chain growth, which collapse upon reaching a critical chain length. The collapsed chains then serve as precursor particles for growth, resulting in a stable microgel.

3. Responsivity and Applications of Hydrogels

3.1. Responsive Hydrogels

Unlike non-responsive hydrogels that are simply swollen in the aqueous phase, responsive hydrogels are distinguished and classified as smart materials due to their stimuli-responsive properties [85,96,110]. Responsive hydrogels have been extensively developed to design tunable structures that respond to stimuli of interest (Figure 3) [2,21,32,49,59,65,72,127,128]. The swelling

degree in hydrogels is an example of the controlling factors when preparing reversibly responsive hydrogels, which can be modified by adjusting polymer hydrophilicity, network elasticity, and charge density [86,87,110,129].

Figure 3. Schematic of a responsive nanogel, where changing temperature, pH, and/or ion in the aqueous phase causes deswelling or swelling of the nanogel.

The swelling/deswelling of polymer networks described by Dusek and Patterson is a fundamental characteristic of responsive hydrogels [110]. In their theoretical estimation, the phase transition of a free swelling gel can be hardly achieved by varying the degree of cross-linking of the polymeric gel and/or dissolved solvent quality, while the phase transition of a polymer network can be achieved easily. Based on their contribution, it might be important to modify the polymer phase transition for the design of hydrogels that are responsive to the adjustment of key factors.

In another study, thermoresponsive ionic gels underwent a discontinuous phase transition of their network, in contrast to a continuous transition by non-ionic gels. It is also interesting to note that the deswelling rate of the ionic gels was inversely proportional to the square of the smallest dimension of the gels [86–88,90,91]. In addition, Yan and Hoffman reported that the polymerization of NIPAm gels at temperatures above the LCST yielded gels with a large pore size [106], which allowed for the production of pNIPAm gels with a rapid swelling rate (Figure 4). In contrast, the hydrogel polymerized at temperatures below the LCST yielded a smaller pore size than that of the hydrogel polymerized above the LCST and had a slower swelling rate. They also suggested that the hydrogel with a large pore size could be useful in drug delivery applications.

Early studies on responsive hydrogels were conducted with the aim of constructing new materials that respond to different stimuli such as pH, temperature, light, and electric field, eventually triggering the phase separation of the polymeric materials [33,84,87,88,94]. For instance, a light-responsive hydrogel was formed by copolymerization of the thermoresponsive monomer NIPAm and the light-sensitive chromophore, i.e., trisodium salt of copper chlorophyllin, with a cross-linking agent, which resulted in the phase transition of the gels upon light illumination [94]. In particular, they developed a visible-light-responsive hydrogel where the polymer network was directly heated by the light, which resulted in a rapid transition rate of the hydrogel. Another example of responsive

hydrogels was shown by applying electric fields to polyacrylamide gels. Herein, an acrylamide group was changed into an acrylic acid group by hydrolysis under electric field, enabling it to provide excess H^+ ions and thereby increasing Coulomb interactions for the volume phase transition of the acrylamide gel [88]. This study showed that the volume change could be either discrete or continuous depending on the ionization degree of the gel as well as the solvent composition.

Figure 4. Swelling kinetics of polyNIPAAm hydrogels prepared at above (filled circles) and below (open circles) the lower critical solution temperature (LCST) [106]. Reproduced from [106] with permission. Copyright 1995 Elsevier.

Further efforts have been put into the successful application of responsive polymeric gels in the field of controlled drug release. First, ionic polymer gels including poly(ethyloxazoline) (PEOX), poly(methacrylic acid) (PMAA), or poly(acrylic acid) gels were utilized to capture insulin in a gel matrix. In response to applied electric current, the insulin-loaded matrix released the insulin outward by disrupting the hydrogen bonding of the responsive gels (Figure 5) [33]. Although this work is impractical for real-world applications, the concept of loadable gels responding to external stimuli has been generally cited by other studies in the field of drug release [35,36,63,130–133].

Figure 5. Insulin release rate of insulin-loaded hydrogels as a function of electric current [33]. Reproduced from [33] with permission. Copyright (1991) Springer Nature.

For responsive hydrogels in chemical sensing, the phase transition of the hydrogels was utilized to construct chemically responsive materials or responsive surface patterns coupled with non-responsive materials [18,21,24,54]. One example of a chemical sensing material is to combine a colloidal array of non-responsive polymer spheres with responsive hydrogels during the polymerization process. The hydrogel matrix can be modified with molecular recognition moieties for metal ions, resulting in swelling in response to metal ions due to an increased osmotic pressure of the hydrogel matrix. Therefore, the swelling increases the distance between non-responsive colloidal spheres and shifts the Bragg peak of the diffracted light [21]. This study suggested that a responsive hydrogel as a matrix could be used to facilitate the detection of metal ions by mediating properties of non-responsive materials (Figure 6). However, there is a caveat to using this technique, which requires a high ionic strength of electrolytes and similarly charged metal ions. Hu et al. reported that a thermoresponsive hydrogel (i.e., pNIPAm) can be used to pattern the surface of a non-responsive gel [18]. In this study, the thermoresponsive hydrogel was transformed by changing the temperature, which switched the patterned area from visible to invisible. A limitation of this technique is that it is hardly reproducible in real-world sensing applications due to the slow switching time of ~10 s.

Figure 6. Diffracted wavelength of a polymerized crystalline colloidal arrays (PCCA) sensor as a function of cation concentrations [21]. Reproduced from [21] with permission. Copyright (1997) Springer Nature.

The construction of active components using different types of responsive hydrogel was reported by the Beebe group [12]. Responsive hydrogels were utilized to create a gate component for controlling microfluidic channels via photo-polymerization, which was accomplished by the swelling or deswelling of the hydrogel gate in response to a fluid stream. Interestingly, they proposed that responsive gels at micron scale would have fast response times due to the short diffusion paths, although their construct was macro-scale with a slow response rate. This suggests that microgels (micron-scale hydrogel particles) would be beneficial for developing advanced applications due to their distinct characteristics in response time.

Responsive hydrogel nanoparticles (i.e., colloidally stable particles in nanoscale) are characterized by their smaller size, higher surface area, and, more importantly, faster response time for the volume phase transition than those of macro-scale hydrogels [134]. Such nanoparticles can be synthesized by a precipitation polymerization method, allowing for the formation of thermoresponsive pNIPAm hydrogel nanoparticles with uniform size distribution. Cross-linking density, solvent, and comonomers influence the volume phase transition temperature (VPTT) of hydrogel nanoparticles just as they influence macro-scale hydrogels [112,113,135]. For instance, the higher content of acrylic acid (AAc) as a

comonomer resulted in a higher VPTT of the hydrogel nanoparticles in temperature ramp experiments while BIS as a crosslinker led to a slight increase of the hydrogel VPTT (Figure 7) [136].

Figure 7. VPTT of hydrogel nanoparticles as a function of AAc and BIS contents in the hydrogel nanoparticles [136]. Reproduced from [136] with permission. Copyright (2018) MDPI AG.

Responsive hydrogel nanoparticles obtained by precipitation polymerization have been extensively investigated for the development of novel responsive materials in upcoming applications. For instance, colloidal crystalline assemblies using thermoresponsive hydrogel nanoparticles were reported which showed tunable phase behavior due to their thermoresponsivity and softness [137–139]. In particular, the behavior of hydrogel crystals was completely reversible through the order–disorder transition in response to temperature changes. The thermoresponsivity of hydrogel nanoparticles allows the crystalline assemblies to be rapidly and widely tunable in response to environment changes including temperature and irradiation. Since the hydrogel nanoparticles experience swelling and deswelling of volume in response to external stimuli, the nanoparticles were utilized to fabricate responsive hydrogel nanoscale optics via electrostatic interactions with no complex fabrication steps [7,10,64,65].

3.2. Bioresponsive Hydrogels

Bioresponsive hydrogels that are subject to change in their structure and morphology in response to a biological stimulus have been demonstrated in a number of applications in drug delivery, tissue regeneration, biosensors, and biomimetic systems [5,21,33–52,57–75]. In contrast to simple stimuli-responsive hydrogels, bioresponsive hydrogels that are coupled to biological moieties have been developed by modifying the polymer composition, polymeric structure, and specific functional groups (Figure 8). In this section, bioresponsive hydrogels will be discussed in terms of the types of structural responses to biological stimuli that they exhibit.

Figure 8. Schematic of a bioresponsive nanogel prepared by conjugating protein, DNA, and RNA to a responsive nanogel.

Bioresponsive hydrogels can be prepared in a degradable form, which is induced by biological cues such as enzymes. Such hydrogels have been researched extensively to develop smart drug delivery systems and tissue regeneration agents [42,59,60,140,141]. In one of these studies, Lutolf et al. reported that hydrogels engineered with an integrin-binding moiety and a matrix metalloproteinase (MMP) substrate were proteolytically degraded by MMP released from human fibroblasts. They also showed that the hydrogel could be used to deliver bone morphogenetic protein-2 (BMP-2) to the defect site in a rat cranium. This could be useful for alternative materials for fibrin or collagen in tissue engineering. Similarly, Kim and Healy reported that degradable pNIPAm-co-AAc hydrogels can be prepared by utilizing the peptide cross-linker and photo-polymerization [142]. In their study, the hydrogels were enzymatically degraded in the presence of collagenase, which was influenced by the concentration of the enzyme and the cross-linking density (Figure 9).

Figure 9. Degradation of peptide-linked pNIPAAm-co-AAc hydrogels with different crosslinkers in collagenase solution [142]. Reproduced from [142] with permission. Copyright (2003) American Chemical Society.

In this category, poly(acrylamide) hydrogels crosslinked with peptides were also developed, which were dissolved in the presence of α -chymotrypsin [140]. Such biodegradable hydrogels have potential applications in tissue regeneration as a scaffold material [59,60]. In this study, the hydrogel network was functionalized with an integrin binding site and substrate for MMP, which provide the capability of binding to cells and degrading the network, respectively. By exposing the hydrogels to human fibroblasts, cell adhesion, followed by the invasion into the network, was seen through integrin-mediated binding and MMP-linked cleavage. The results suggest that the development of advanced hydrogel systems opens the possibility not only for fundamental studies on cell–matrix interactions but also for biocompatible materials for tissue regeneration. Biodegradable hydrogels with a different application were reported for use in drug delivery where a drug was released by changing the conformation of the hydrogel network [42]. Herein, hydrogels equipped with peptide cross-links were loaded with a chemotherapy drug, which was released by enzymatic cleavage in the presence of MMP (Figure 10).

Figure 10. Schematic of cancer chemotherapeutic hydrogel matrixes (a) obtained through the complexation of platinum and aspartic acid linked to peptides in the network (b) and their release from hydrogel matrixes (c) [42] (Reproduced from [42] with permission. Copyright 2005 American Chemical Society). MMP: matrix metalloprotein. CDDP: cisplatin.

Another type of bioresponsive hydrogel could be the biologically inspired gels that mimic biological functions by displaying a specific interaction with a biological moiety. These studies are well described in the fields of cell targeting, protein sieving, and functional substrates to prevent or enhance cell adhesion [49,53,58,143]. This kind of bioresponsive hydrogel can be prepared by employing biological pair molecules to the hydrogel network, which allows for the binding of receptors and antibodies to ligand- and antigen-modified hydrogels, respectively. For instance, such hydrogels were used as a targeted drug delivery carrier, where hydrogel nanoparticles were functionalized with folic acid for targeting cancer cells [49]. In this study, the hydrogel nanoparticles were efficiently incorporated into cancer cells through folic acid and its receptor-mediated endocytosis (Figure 11). Similarly, hydrogel nanoparticles were made more sophisticated with both degradable and biological binding capabilities. Nayak and Lyon synthesized core-shell hydrogel nanoparticles by the “seed and feed” method, where the core was conjugated with a ligand and the shell was formed with chemically degradable cross-links. Here, the degradable shell of hydrogel nanoparticles was used to filter proteins by the pore size and then the ligand-labeled core for further binding [53]. These results suggest that the manipulation of the cross-linking density of the hydrogel shell enables one to not only filter proteins of a particular size, but also to reduce the nonspecific binding of larger proteins.

Figure 11. Schematic of targeted pNIPAm hydrogels for cancer cells. The hydrogels are engineered by folic acid to bind with folate receptors on cancer cells [49]. Reproduced from [49] with permission. Copyright (2004) American Chemical Society.

Other studies investigate hydrogels which are reversibly responsive to biological stimuli, where they undergo a change in volume and/or optical property. One potential application of reversibly bioresponsive hydrogels is the construction of biomolecular sensors where a physicochemical change of the hydrogel is observed to determine the binding event of proteins, oligonucleotides, or small molecules [2,21,64,65,72,144]. Biomolecular sensing using bioresponsive hydrogels is an example of advanced applications that utilize changes in the optical properties of hydrogels to measure a protein or oligonucleotide binding event. In addition, reversible changes in the properties of bioresponsive hydrogels were demonstrated by engaging antigens and antibodies together into a hydrogel network, providing conceptually breakable and reversible cross-links through antigen–antibody binding [2,71,72,144]. Unlike chemical cross-links, the strength of this bond could be adjusted by changing biomolecule pairs that have a broad range of affinity from μM to pM .

When exposed to free-antigen solution, the antigen–antibody cross-links in the hydrogel network could be disrupted by competitive binding of the free antigen, resulting in the reswelling of hydrogels due to a decrease in the degree of cross-linking. Alternatively, the hydrogels could undergo reversible volume change when exposed to a buffer solution by reformation of the cross-link due to the release of bound free antigen. Similarly, a bioresponsive hydrogel was utilized to recognize tumor-specific marker glycoprotein (i.e., α -fetoprotein (AFP)), where the hydrogel was constructed using the imprinting of a lectin–AFP–antibody complex [2]. Here, the imprinted hydrogel displayed a response to the tumor marker by decreasing volume in the presence of the AFP (Figure 12).

In spite of these interesting studies, there are remaining issues. For example, the response time is very slow, ~ 1 h, and the volume change is small, about 5%, which hamper the applications of the hydrogel system for real-world applications. Such limitations could be improved by using nanosized hydrogel systems because nanogels have a faster phase transition time than bulk gels. For instance, bioresponsive nanogels were utilized to functionalize the gold surface of a biochip for surface plasmon resonance (SPR) analysis, where responsive nanogels were conjugated with an immune check-point protein (i.e., PD-1), and PD-1 antibody was measured with high selectivity [144]. This work demonstrated that responsive nanogels could be used not only to recognize the molecular mechanism of protein binding, but also to screen a target antibody in biological media (Figure 13).

Figure 12. Swelling behavior of α -fetoprotein (AFP)-imprinted hydrogels in the presence of free AFP in solution [2] (Reproduced from [2] with permission. Copyright (2006) National Academy of Sciences.) PAAm: poly(acrylamide).

Figure 13. Schematic of an antibody-responsive nanogel and its application for surface plasmon resonance (SPR) analysis.

4. Conclusions

In this review, we introduced and discussed responsive hydrogels, particularly bioresponsive nanogels that allow for the design of a novel platform in which responsivity is correlated with a specialized task in response to a biological event. The composition of and synthetic methods for the achievement of bioresponsive nanogels were discussed, linking them with the responsivity of the nanogels. Then, a number of applications using responsive and bioresponsive hydrogels were reviewed to present the utility of these materials in many fields. While these hydrogels and nanogels have been successfully applied for novel biological applications, including controlled drug delivery systems, biosensing, and tissue engineering, they are still of great interest for developing more sophisticated nanogels that have specialized capabilities with more complex responsivities.

Author Contributions: Conceptualization, H.C.; investigation, H.C., S.J., J.Y., S.Y.B., and D.K.; resources, H.C., S.J., J.Y., S.Y.B., and D.K.; data curation, H.C., S.J., J.Y., S.Y.B., and D.K.; writing—original draft preparation, H.C., S.J., J.Y., S.Y.B., and D.K.; writing—review & editing, H.C.; supervision, H.C.; project administration, H.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Acknowledgments: We acknowledge the intern program of Scholar Foxtrot Co., Ltd.

Conflicts of Interest: The authors declare no conflicts of interest.

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