Pros and Cons: Supramolecular or Macromolecular: What Is Best for Functional Hydrogels with Advanced Properties?

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Hydrogels are fascinating soft materials with unique properties. Many biological systems are based on hydrogel-like structures, underlining their versatility and relevance. The properties of hydrogels strongly depend on the structure of the building blocks they are composed of, as well as the nature of interactions between them in the network structure. Herein, gel networks made by supramolecular interactions are compared to covalent macromolecular networks, drawing conclusions about their performance and application as responsive materials.

1. Introduction

Herein, we lay out the pros and cons of constructing (hydro) gels from polymer networks held together by noncovalent interactions or covalent bonds. Hydrogel materials currently find many applications in personal care products, biomaterials, coatings, and plant fertilizers. They have a large potential for future application in sensing, drug delivery, soft robotics, and biohybrid or biointerfacing materials. To scientists working in those fields, the choice of material type may depend heavily on the intended application and associated required properties. There, it can be useful to consider a generalized overview and comparison of hydrogel structure, properties, and performance in various scenarios.

Historically, it has been difficult to provide a comprehensive definition of a gel, but the one by J. D. Ferry suits our purpose: “Gels are defined as a substantially dilute cross-linked system, which exhibits no flow when in the steady-state.”[1] It contains a network-forming minority component as well as a majority swelling agent. In the case of a hydrogel, the swelling agent is water. As such, many biological structures and tissues can be considered hydrogels. The network-forming component can have many origins and structures, including particles, crystallites, polymers, proteins, and small molecules. The important requirement for the formation of hydrogels using above-mentioned building blocks is their ability to form physical or chemical crosslinks to form a network-like structure. In this viewpoint, we will address and compare two widely investigated and applied gel classes, i.e., macromolecular hydrogels (MHGs) and supramolecular hydrogels (SHGs). Both types have been extensively reviewed[2] in recent years. It is not the objective of this viewpoint to add another exhaustive review, but rather to provide insight into the opportunities and limitations of both hydrogel types in particular scenarios. One of the conclusions will be to arrive at hybrid systems using advantageous properties of each approach to create truly advanced soft materials.

2. Supramolecular or Macromolecular Functional Hydrogels?

2.1. Structure and Basic Properties of Hydrogels

MHGs contain a physically or covalently crosslinked amorphous polymer network. Crosslinks can be introduced during polymerization using a multifunctional monomer (crosslinker), or through chemical post-modification reactions on existing polymers. A typical example of MHG formation is the radical polymerization of acrylamide with N,N′-methylenebis(acrylamide) crosslinker (0.5 mol%) in water, giving after 10–15 min a transparent hydrogel with a swelling ratio of 13.3 and E-modulus of 0.03 MPa (Figure 1). SHGs have a network made up of low-molecular-weight molecules, oligomers, or polymers that self-assemble on timescales of minutes to hours into larger, often fibrous or otherwise somewhat ordered, superstructures through noncovalent interactions.[3] Subsequent crosslinking through noncovalent interactions, entanglement, or covalent means then leads to gelation. A typical example here is the protonation-induced self-assembly and subsequent gelation of hydrophobic dipeptide derivatives in water, giving stiff transparent gels with low yield stress (Figure 1).[4] A third class of hydrogels is an...
intermediate between SHGs and MHGs, consisting of an amorphous network of polymer chains crosslinked using noncovalent interactions (Figure 1). In some scenarios, these supramolecular gels (SMHGs) act more as MHGs (e.g., regarding mechanical properties[8]), in others more as SHGs (e.g., reversibility[9]). In all approaches, crosslink density has a large impact on many properties of the resulting gel, such as mesh size and stiffness.[10] For MHGs, control over crosslink density is straightforward and predictable as it relates to the ratio of introduced crosslinker monomer or the extent (yield) of the crosslinking chemical reaction. For SHGs control over crosslink density is much less predictable as these crosslinks are often somewhat dynamic, their strength can depend on many environmental factors and can also be influenced through processing steps and the kinetics of network formation.[8] A higher level of control over crosslink density can be achieved by having covalent[9] crosslinks between fibers, leading to remarkable mechanical behavior (strain stiffening). Alternatively, the use of highly specific and programmable noncovalent crosslinking interactions based on, e.g., that DNA can generate responsive hydrogels with cell interactions that depend on the material superstructure.[10]

Hydrogels are soft materials with an open porous structure and high water content.[11] As such, they have many properties that align with those of biological tissues, leading to many current and future applications in biomedical or bioinspired materials.[12] In the development of those applications we also see a tendency to substitute static, permanent gel materials by more dynamic or reversible, responsive, and interactive gels with transient programmable properties. In these various circumstances, gel performance can depend on static as well as dynamic properties, and choice of material also depends on ease of design, synthesis, and functionalization. Considering these specific requirements, MHGs and SHGs may show stark differences in properties, performance, and applicability. We will discuss several considerations here illustrated by recent examples.

2.2. Chemical Design of Hydrogels

The design and synthesis of hydrogels are first important steps to target various applications. The synthesis approaches for MHGs and SHGs are hugely different because of the different mechanisms of gel formation. In the majority of the cases for MHGs, gelation is based on covalent network formation starting from often readily available soluble monomers or prepolymers and crosslinkers. The formation of MHGs can be realized by the polymerization/crosslinking of monomers[13] or crosslinking of prepolymers.[14] Using the second approach, one may benefit from low reaction temperatures, avoid residue of nonreacted monomer, and benefit from shorter gelation times (5–15 min), which is very important for biomedical applications of hydrogels.[15] As such, MHGs formation and certain mechanical properties are largely predictable from the amount and nature of the monomers or prepolymers and the crosslinker content. New functional groups can be introduced in the network by adding small amounts of functionalized monomers to such conventional gelation mixtures, as long as these functionalized monomers are compatible with the used polymerization procedure.[16] Alternatively, the new functional groups can be integrated into the prepolymer structure before or after hydrogel formation.[17] The chemical structure of the crosslinking agent may influence the network topology ( bifunctional vs multifunctional crosslinkers) or introduce specific functions to hydrogels like degradability (e.g., redox- or mechano-cleavable disulfide bonds; enzyme-cleavable ester and amide bonds), re-shaping and self-healing (supramolecular bonds like host–guest complexes, H-bonds), or toughness and elasticity (ionic bonds).[18]

For SHGs, both gelator structure and crosslink density can be extremely difficult to predict.[19] The ability to self-assemble into a network has to be built into the monomers (or “gelators”). Gelators are often not commercially available and have to be synthesized. The ability to assemble can be extremely sensitive to the introduction of other functional groups in the gelator. These constraints can put substantial structural limitations on the design of SHGs. Still, tethering a functional group to a small amount of gelator through a long soluble spacer will often allow decoration of gel fibers.[20] For both MHGs and SHGs, one can include click chemistry functionalities in the network-forming mixture, for post-gelation decoration of the network.[21]
2.3. Network Structure of Hydrogels

The sequence structure of the polymers making up the MHG network is commonly random when starting from a mixture of monomers. The use of sequence controlled macromonomers (e.g., block copolymers) is the preferred method to introduce internal structure in the gel network. After network formation, the chemical composition of polymer chains and distribution of crosslinks in MHGs are fixed. This can be quite the opposite in SHGs, where monomer (gelator) exchange dynamics (on the second to hour timescale\(^{[22]}\)) within the fiber are mainly dictated by interaction strength. Several cases now exist where, either before or after initial network formation from a mixture of gelators, the gelators selectively form interpenetrating\(^{[23]}\) or phase-separated networks\(^{[24]}\) of homopolymer fibers through a self-sorting process. Similarly, driven by the combination of dynamics, bond exchange, and interaction strength, potent gelators can self-select from a mixture of interchanging gelator precursors.\(^{[25]}\)

Spatial differentiation in hydrogel materials is classically achieved through patterning, most commonly using light and masks. For MHGs, post-gelation functionalization is preferred as the diffusion is stopped in the gel state.\(^{[21b,c]}\) Analogous approaches exist for SHGs,\(^{[26]}\) but there are also examples of pre-gelation spatial differentiation in SHGs, through localized gelator formation using, e.g., light, electrochemical potential, seeding surfaces, or local catalysts as a spatially resolved stimulus.\(^{[27]}\) An entirely different method for spatial differentiation is by reaction diffusion, and this is an example where the worlds of MHGs and SHGs meet. Controlled reaction and diffusion of SHG gelator precursors can lead to SHG object and pattern formation,\(^{[26d,28]}\) as well as the stabilization of emulsions,\(^{[29]}\) typically on timescales of hours to days depending on diffusion lengths. Diffusion is often carried out inside an MHG, leading to the formation of MHG–SHG interpenetrated network hybrid gel materials. Inversely, a recent example shows damage repair in bulk polymer materials by first forming a supramolecular gel network in the crack, that then acts as a medium for the diffusion and reaction of polymerization monomers, making up the final network.\(^{[30]}\) Although not a hydrogel, it does demonstrate the power of combining supramolecular and macromolecular network formation.

2.4. Functional and Responsive Hydrogels

Since hydrogels are very attractive materials for numerous applications, their structure and morphology need to be tailored to enable specific properties and functions. The mechanical properties of hydrogels are extremely important for their use in medical materials and devices.\(^{[31]}\) One such property is shear thinning, and recovery after removal of the applied stress. This behavior can allow application as tissue engineering scaffolds or injectable hydrogels, for subcutaneous drug delivery. There, after shear-induced transition to the sol state, the gel network rearranges and re-forms. In SHGs, this effect is observed in a limited number of cases as fiber and monomer exchange dynamics are often too slow to obtain the effect.\(^{[32]}\) True self-healing (for instance after cutting a gel into pieces) is very rare for SMGs.\(^{[33]}\) For MHGs, the permanent nature of MHG networks generally prevents self-healing entirely. An important exception is the use of reversible crosslinks, either in SMHGs using noncovalent interactions,\(^{[34]}\) or in MHGs using dynamic covalent bonds. There, covalent crosslinks can exchange continuously or after a stimulus, rearranging the network. SMHGs and dynamic covalent MHGs are often capable of self-healing after damage, recovery after shear-thinning, or remodeling their network to release an applied stress.

Mechanical properties such as tensile strength, elasticity, extensibility, and toughness are important for numerous applications. It is important to note that larger is not necessarily better: for instance, when used as a tissue engineering scaffold, a property such as the gel storage modulus should be somewhat matched to that of the tissue and certainly not be as high as possible. Where for SHGs, these properties are difficult to predict or tune, for MHGs they can be tuned through the amount and distribution of crosslinks and chemical structure of functional groups integrated into polymer chains. Pushing the boundaries of mechanical properties of hydrogel materials, Gong and co-workers recently introduced a new family of SMHGs, which exhibit high mechanical strength and extreme elasticity. Their hydrogels consist of amphiphilic polymer chains crosslinked by ionic or a combination of ionic and covalent crosslinks (Figure 2).\(^{[16]}\) These so-called polyampholytes, bearing randomly distributed cationic and anionic groups along the polymer chain, form extremely tough and viscoelastic hydrogels. The random
distribution of charges provides ionic bonds with a wide distribution of strength, where the strong bonds serve as permanent crosslinks, imparting elasticity, whereas the weak bonds reversibly break and re-form, dissipating energy. The Young’s modulus and swelling degree of these SMHGs with supramolecular crosslinks can be tuned over a wide range by using combinations of different ionic monomers and tuning their concentration \( C_m \) during the polymerization process (Figure 2).

Degradation of hydrogels is an extremely important aspect if they are used as delivery systems, implant coatings, or scaffolds. Hydrogel degradation is a complex process where both the hydrogel structure and environment are changing with time. It includes changes of the network structure and simultaneous release of degradation products (small molecules, oligomers etc.). Very few systematic studies of hydrogel degradation processes have been reported.[37] MHGs and SHGs are different in their degradation behavior and nature of degradation products. Basically, if MHGs contain degradable or supramolecular crosslinks, they degrade to the (mostly) linear soluble oligomer chains.[18b,38] If the hydrogels consist of polymer chains with cleavable bonds in the main chain, then degradation may result in the formation of a mixture of small molecules and branched oligomers.

Contrary, the largest molecular unit in an SHG is the gelator molecule itself. Fiber-bound gelators are in dynamic equilibrium with gelators that are free in solution. Degradation of SHGs can proceed via three pathways, often simultaneously. Depletion of gelator molecules in solution will lead to fiber breakdown. Mechanical forces can cause breaking of fibers, and fiber fragments can then leave the gel. Sometimes it is possible to either breakdown a gelator molecule (commonly through hydrolysis, analogous to biodegradable MHGs) or change its gelation ability through a chemical reaction (e.g., (de-)protonation, redox), both leading to fiber destabilization. The latter is an interesting example where SHGs are stimuli-responsive, leading to advanced functions in, for instance, drug delivery.

Stimuli-responsiveness is one of the attractive properties of hydrogels, which is useful for the fabrication of hydrogel actuators, dosing devices, and sensors. The classical way to implement stimuli-responsiveness into MHGs[39] is the incorporation of temperature-responsive (leading to lower critical solution temperature (LCST) or upper critical solution temperature (UCST) behavior) or pH-responsive monomers in the polymer chain.[40] Recently, the utilization of light as stimulus emerged, by the incorporation of photo-switchable molecules (azobenzenes, spiropyrans, donor–acceptor Stenhouse adduct (DASAs), etc.) as side groups into polymer chains.[41] In the case of isotropic MHGs, stimuli such as temperature, pH, or light lead to the reversible change of the volume and swelling degree. Anisotropic MHGs can perform complex shape changes, which is useful for the fabrication of swimmers or robotic devices.[42]

In SHGs, changes in the gelator structure often induce a response in the properties of the gel. As there are many ways to change the gelator structure (chemical bond formation...
or destruction, complexation, protonation, photochemical isomerization, etc.), gels responding to a very broad range of stimuli have been reported.[2d,43] However, the range in resulting responses is substantially smaller than for MHGs, with the majority leading to a sol–gel or gel–sol transition.[44] A few exceptions include thermo-induced gel-to-gel transitions,[45] chemical-reaction-induced viscosity changes,[25a] and light or charge-transfer-induced changes in optical properties.[46] The reason for this typical phase change response is that such a change in gelator structure often has a drastic positive or negative impact on its ability to form a gel. Also, because of limited elasticity of typical SHG fibers, mechanical stress, changes, or perturbations often lead to gel collapse instead of expansion, deformation, or actuation as one may see for MHGs. Still, these stimulus-induced phase transitions find many applications, for instance in controlled drug release,[47] catalysis,[48] switchable membranes,[49] in interactions with biological structures,[2c] or as sensors.[50]

Although stimulus response can be programmed into hydrogels, more advanced functions such as autonomous multi-stimuli response (logic gates, computing), or self-regulation of gel structure and properties, are still out of reach. These are all typical features seen in some advanced biological hydrogels. An interesting example of such an advanced biological hydrogel is fibrin. Fibrin is responsible for the clot formation and fast termination of bleeding caused by injury, which is an essential function for mammalian organisms. Fibrin is formed when needed by hierarchical self-assembly and eventually covalent crosslinking of peptide fibrinogen triggered by the enzyme thrombin (Figure 3).[51,52] The final fibrin network consists of long fibrillar structures which are crosslinked by covalent and supramolecular bonds. Remarkably, this fiber-like structure of fibrin is responsible for the strain-stiffening behavior of the hydrogel, which is required to resist and efficiently terminate blood flow.

3. Conclusion

The example of fibrin hydrogels demonstrates that the hierarchical assembly of covalent and supramolecular bonds in combination with the use of molecular (amino acids, peptides) and macromolecular (proteins) building blocks is required to ensure advanced properties and specific functions. Biological hydrogels are frequently composed of macromolecular and low-molecular components, containing covalent and noncovalent crosslinks, and are assembled in a modular way exhibiting different hierarchy levels. Such materials often exhibit hysteresis effects and nonlinearity of their properties, which are essential to functions like adaptability and time-programming. Finally, many biological hydrogels can regenerate through continuous growth, solving a problem related to destruction or damage caused by bacteria or inflammation processes. At present, the performance of synthetic hydrogel materials is not on par with these advanced biological hydrogels. Synthetic MHGs and SHGs each have areas where they outperform the other, and individually start to show some of the base principles and properties needed to reach the level of biological hydrogels. So, merging of the two worlds (MHGs and SHGs) seems to be an optimal way to design life-like adaptive soft hydrogel materials.

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Conflict of Interest

The authors declare no conflict of interest.
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