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Review

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Gels: From Soft Matter to BioMatter

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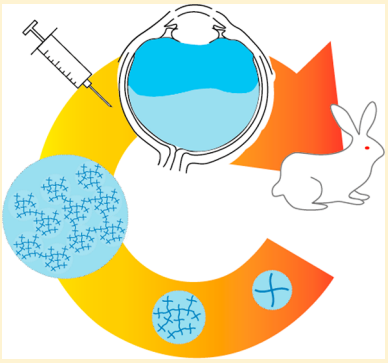
ABSTRACT: Progress in the investigation of soft-matter gels is discussed, and cutting-edge applications of BioMatter are demonstrated. Emphasis is placed on a series of high-performance hydrogels consisting of tetra-arm poly(ethylene glycol), called "Tetra-PEG gels". Tetra-PEG gels are now well known for their extraordinarily uniform and monodisperse network structures, compared with those of conventional gels, and can be tuned depending on the given molecular weight, concentration, choice of pair prepolymers, hydrophilicity/hydrophobicity, thermosensitivity, composition, etc. The unique characteristics of Tetra-PEG gels are reviewed, and a variety of applications are demonstrated. Problems in their biomedical application are then raised, followed by a discussion of attempts to circumvent these issues.



1. INTRODUCTION

Gels are ubiquitous substances that humans have been using in foods, glues, paints, and so on since prehistoric times. In the 1930s and 1940s, gels began to be realized as useful "matter" owing to the development of polymer science, through the molecular theories of polymers[1−3] and gel swelling.[4] This concept was readily applied to responsive gels by Kuhn and Katchalsky in 1950.[5] They observed repeated swelling/shrinking in cross-linked poly(acrylic acid) gels upon changing the pH. Since then, the interplay between the science and technology of gels has progressed, as shown in Figure 1. One example is soft contact lenses. Wichterle and Lim developed hydrophilic cross-linked 2-hydroxyethyl methacrylate (HEMA) hydrogels in 1960,[6] which opened the door to applications to soft contact lens. Hard contact lens, developed in the 1950s, were made of bulk poly(methyl methacrylate) and had several limitations, including oxygen permeability. HEMA is regarded as one of the first biological/medical applications of hydrogels. Superabsorbent polymers (SAPs) were developed in the 1970s and commercialized at the beginning of the 1980s. Today, SAPs are ubiquitous in daily life, not only in diaper and sanitary goods but also in useful materials applied in civil engineering and agriculture.[7]

In the 1960s, Dusek and Patterson predicted a discrete volume change in a gel,[8] which was experimentally discovered by Tanaka in 1977, called the "volume phase transition" in polymer gels.[9] This led to numerous applications of various types of stimuli-responsive gels in the 1980s, for example, pH-sensitive and temperature-sensitive gels,[10] photosensitive gels,[11] and so on. An extensive review of the volume phase transition of gels was given by Shibayama and Tanaka, which overviewed the development of the theory, structure, physical properties, and applications of gels.[12] These gels are also called responsive gels, smart gels, or intelligent gels, and more extensive applications were developed in the 1990s,[13] particularly with respect to biomedical applications, such as drug-delivery systems,[14] chemo-mechanical actuators,[15] sensors, and rapid swelling/shrinking (fast release) gels.[16,17] In 1997, Jeong first reported biodegradable injectable block copolymers for drug-delivery systems.[18] The basic scientific understanding of gels, such as percolation,[19,20] entanglements,[21] and inhomogeneities,[22,23] was further advanced in the 1970s and afterward. Entering the 21st century, the fabrication of high-strength gels was pursued and resulted in discoveries of novel high-strength gels, namely, slide-ring gels,[24] nanocomposite gels,[25] and double network (DN) gels.[26] These gels have changed the concept of gels from soft-and-fragile matter to soft-and-tough matter.[27]

Despite the long history of gels (as shown in Figure 1), the realization of ideal networks/gels free from defects and entanglements has not been achieved. In 2008, however, Sakai and co-workers succeeded in fabricating a gel, called tetra-arm-poly(ethylene glycol) gel (Tetra-PEG) gel, which has an extraordinarily more homogeneous network structure than any other gels known so far.[28] Tetra-PEG gel is a high-strength chemical hydrogel with elastic modulus comparable to that of native articular cartilage, and it is stable in the body. The gel

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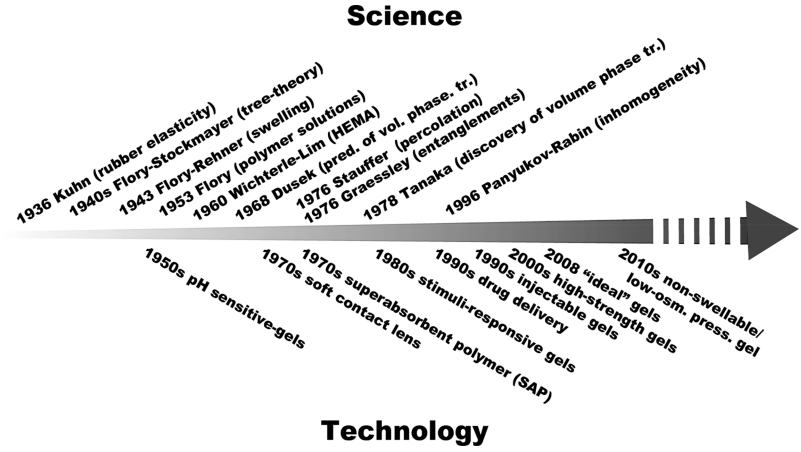

Figure 1. History of the development of the (upper) science and (lower) technology of gels.

was made via "cross-end-coupling" of two types of Tetra-PEGs with complementary functional end groups. Tetra-PEG gels enabled us to fabricate tough gels[28,29] to re-examine the theory of rubber elasticity,[30] to prepare defect-controlled gels,[31] and so on. Figure 2 shows the evolution of the number of papers on

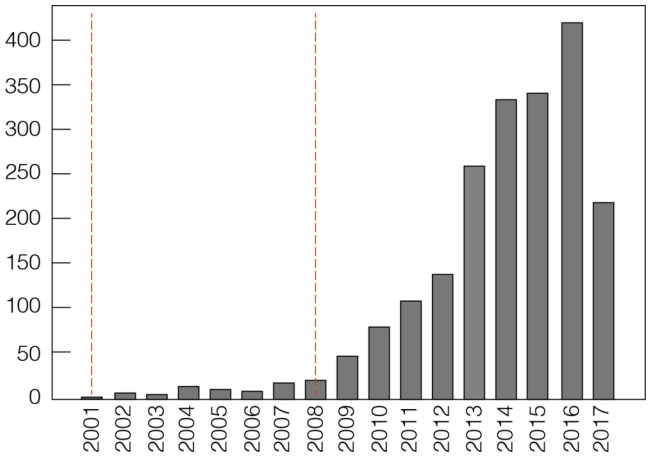

Figure 2. Evolution of the number of papers on Tetra-PEG gels (Web of Science, as of June 20, 2017, surveyed with the keywords (tetra-PEG OR tetraPEG OR tetra PEG gels OR tetra-poly(ethylene glycol) OR tetra-poly(oxymethylene)).

Tetra-PEG gels, which has been increasing rapidly since 2008. This figure eloquently addresses the paradigm shift Tetra-PEG gels have caused in gel science. It should be noted, however, that Wallace et al.[32] gave the first report on Tetra-PEG gels, although its impact was limited to the medical science community, where Tetra-PEG was applied as sealant in surgery.

Recently, we recognized that the exploration of perfect network gels is not the right direction for biomedical applications of gels. Let us consider a gel implanted in the body. The gel may undergo swelling in the body, followed by degradation due mainly to nonspecific cleavages of network strands, such as oxidation by active oxygen and/mechanical stress.[33,34] Gel swelling is harmful to the surrounding tissue and could cause damage. Subsequent degradation leads to further swelling and spreading of fragmented and/or degraded chemical species. Sakai et al. recognized these significant and serious problems and proposed a new strategy for the fabrication of biofriendly gels.[35] In this Review, we give an overview of the development of Tetra-PEG gels as a typical example of soft matter, followed by proposals of a new class of Tetra-PEG gels and their derivatives for potential biological/medical applications. With an eye toward the future advancement of biocompatible gels, we propose the term "BioMatter", which is coined by combining the words "biology" and "matter" but specifically describes biocompatible/biofriendly materials.

2. TETRA-PEG GELS: NEAR-IDEAL POLYMER GELS

Tetra-PEG gels are fabricated by the cross-end-coupling of amine-terminated tetra-arm-PEG (TAPEG) and *N*-hydroxy-succinimide (NHS)-terminated tetra-arm-PEG (TNPEG) in aqueous media (Figure 3a).[28] These terminal groups undergo

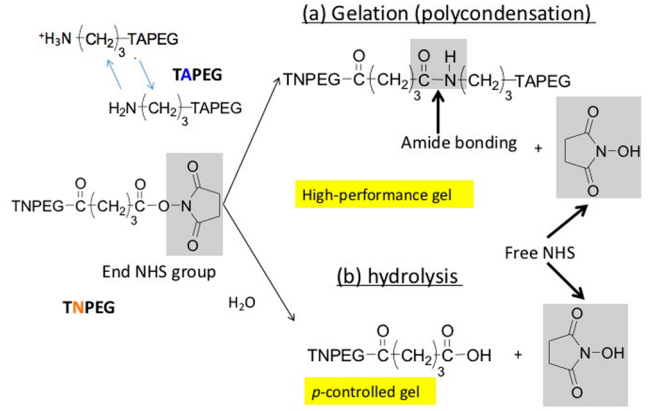

Figure 3. Reaction scheme of (a) condensation ("high-performance" gel) and (b) hydrolysis ("*p*-controlled" gel).

amide condensation, leading to the formation of a three-dimensional polymer network. By tuning the concentration to be near the chain-overlap concentration and the reaction rate to be relatively slow, an exclusive reaction between TAPEG and TNPEG occurs, and a polymer network with negligible amounts of defects, such as dangling chains and entanglements, is formed ("high-performance" gels).[36] The reaction rate can be controlled by the pH, since protonated TAPEG does not react with TNPEG.[37] A series of (1) structural analyses by small-angle neutron scattering (SANS)[38,39] and (2) studies of mechanical properties[36] showed that the Tetra-PEG gels consist of uniform networks with a negligible amount of defects. Furthermore, (3) studies of gelation kinetics[37,40,41] by

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monitoring free NHS groups via IR and UV spectroscopy (Figure 3a) showed that the cross-end-coupling kinetics of Tetra-PEG prepolymers follows a reaction-limited second-order reaction. In addition to condensation, TNPEG gradually undergoes hydrolysis in aqueous media, where free NHS molecules are released (Figure 3b), and TNPEG loses its reactivity for cross-end-coupling. Using this tunable connectivity of Tetra-PEG gels (Figure 3b), "*p*-controlled" gels can be prepared, where p ($0 \leq p \leq 1$) is the degree of cross-linking. This "*p*-controlled" gel fabrication method allowed us to extend our studies to (4) the structure and dynamics of defect-controlled networks,[30,31] (5) the examination of rubber elasticity theories for imperfect networks,[30,42] (6) the critical dynamics at the gelation threshold,[43] etc. Furthermore, owing to the flexibility of the combination of A and B functional groups, the synthesis of Tetra-PEG gels can be carried out not only in aqueous media but also in organic solvent or ionic liquids.[44,45] This allows a wide range of fundamental studies on Tetra-PEG gels and various potential applications from tough gels to nonvolatile gels,[44] molecular sieves,[46] and so on.[47]

3. BIOLOGICAL/MEDICAL APPLICATIONS

There are a number of highly cited review papers on biological/pharmaceutical applications in the literature, for example, "Physicochemical foundation and structural design of hydrogels in medicine and biology",[48] "Thermosensitive sol−gel reversible hydrogels",[49] and "Injectable hydrogels as unique biomedical materials".[50] In these reviews, thermo-reversible hydrogels are described as potential candidates for biological/pharmaceutical applications. Thermo-reversible hydrogels are in the sol state before implantation/injection (or at normal temperature), but they transition to the gel state after implantation in the body (or during fever). Because of these unique properties, we are tempted to regard thermo-reversible hydrogels as the most suitable materials for injectable gels. However, there are a number of fatal problems: (1) reliability (the physical and mechanical properties are not so reliable in the body), (2) toxicity and durability (these gels may easily dissolve and/or degrade in the body), and (3) osmotic pressure (control of the osmotic pressure in vivo is difficult or impossible). These serious problems restrict their applicability. In this section, we consider these problems and propose a new strategy by designing Tetra-PEG gel derivatives for biomedical applications.

Non-swellable Gels. Conventional hydrogels swell under physiological conditions. As a result, their mechanical properties are weakened, and gel swelling causes damage to the surrounding tissues. Amphiphilic co-networks (APCNs), which are composed of hydrophilic and hydrophobic polymers, are candidates for solving this problem, as the hydrophobic component is expected to reduce gel swelling.[51,52] Kamata et al. attempted to develop non-swellable injectable gels.[53−55] First, they prepared Tetra-PEG-PEMGE APCN gels (Figure 4) and studied their shrinking kinetics.[54] Here, PEMGE is an abbreviation for poly(ethyl glycidyl ether-*co*-methyl glycidyl ether). The Tetra-PEG-PEMGE gel showed a practically homogeneous co-continuous structure and resulted in rapid phase transition above the lower critical solution temperature (LCST) of PEMGE, resulting in a shrunken phase. It should be noted that a rapid transition to the swollen phase also occurred when the temperature was reduced to below the LCST. The researchers then succeeded in the fabrication of a "non-swellable" hydrogel by tuning the composition of the hydrophilic and thermoresponsive polymer units, i.e., Tetra-PEG-PEMGE. The gel maintained a rather constant size in the temperature range of 25−40 °C.[55] Furthermore, the gels exhibited no mechanical hysteresis during repeated stretching. Nakagawa et al. carried out the structural analysis of APCN gels with SANS and reported the following:[56] (i) The structure of the hydrogel was similar to that of ordinary Tetra-PEG hydrogels at temperatures below 16.6 °C, whereas discrete spherical domains were formed at temperatures above 19.5 °C. (ii) The number of prepolymer units contained in one domain was much larger than unity, indicating that multiple thermoresponsive prepolymer units as well as Tetra-PEG units aggregated to form a domain. (iii) The formation of domains much larger than a single prepolymer unit led to significant frustration of the matrix polymer network outside the domains, and this frustration enhanced the elastic energy of the matrix network, which lowered the osmotic pressure of the gel and induced significant macroscopic shrinking.

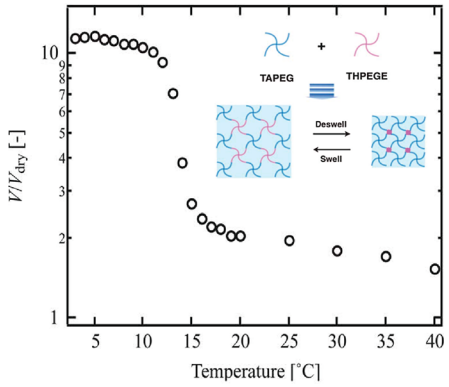

Figure 4. Swelling/shrinking curve and schematic drawing (inset) of a non-swellable gel. THPEGE stands for tetra-OH-functionalized PEGE (TPEGE-OH), which is the thermoresponsive component. Upon heating, PEGE components gradually shrink/swell. Reproduced with permission from ref 53. Copyright 2012 The Royal Society of Chemistry.

Fuse-Linked Gels and Amphiphilic Co-networks. Structural biomaterials need to maintain steady and sufficient material properties in aqueous environments for a reasonably long period of time. Most self-healing gels are not reliable in physiological conditions.[57,58] In particular, under frequent repeated deformation, their mechanical properties continuously degrade over time, as the self-healing process usually takes at least several hours. Furthermore, in physiological conditions, swelling occurs, leading to a decrease in the effective cross-link density. Kondo et al. introduced a "fuse", commonly used in electric circuits, to polymer networks.[59] As schematically shown in Figure 5, the fuse (red points and line) breaks upon the application of a large load prior to the breakage of the main polymer network chains (blue lines) but recovers after the load is released. Since hydrophobic interactions are the driving force for rejoining the fuse, it does not require high thermal energy, and rejoining occurs rather spontaneously upon release of the mechanical strain. Here, the rejoining energy is in a range that is higher than the thermal fluctuation energy but lower than the dissociation energy of covalent bonds. This mechanism was realized by introducing hydrophobic segments into the network, i.e., co-networking. As a matter of fact, Kondo et al. developed an APCN hydrogel with a new molecular design by cross-linking hydrophilic poly(ethylene glycol) (linear-PEG)

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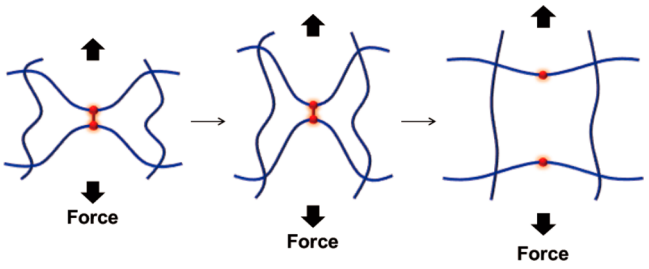

Figure 5. Schematic representation of the "fuse link" concept in fuse-linked gels. The red lines connecting two network chains (blue) are fuse links. Upon the application of stress (thick arrows), the fuse links preferentially break prior to the covalent bonds in the network strands and resolve the local stress concentration (right). Reproduced with permission from ref 59. Copyright 2015 Wiley-VCH Verlag GmbH & Co.

and hydrophobic poly(dimethylsiloxane) (linear-PDMS) prepolymers using a "prepolymer" cross-linker (Tetra-PEG). Figure 6 shows the stress–elongation curves of the "fuse-linked" gel during 100-cycle stretching measurements in aqueous conditions. This fatigue test demonstrates the reliability of the "fuse-linked" gel against repeated mechanical loading. The presence of "fuse" domains was confirmed by SANS.[59,60] It should be noted that the mechanism reinforcing the mechanical properties to form "reliable gels" is very different from that of DN gels, because the original network structure is strongly destroyed by the first stretching in the case of DN gels and the origin of the mechanical toughness is due to its large dissipation energy. This mechanism is called sacrificial bonding.[61]

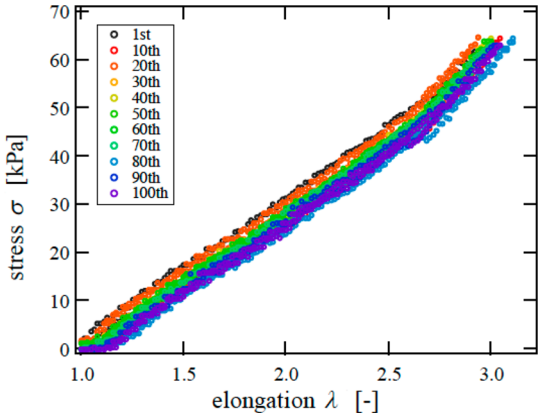

Figure 6. Stress–elongation curves of the fuse-linked gels during 100-cycle stretching measurements. Reproduced with permission from ref 59. Copyright 2015 Wiley-VCH Verlag GmbH & Co.

Critical Clusters. So far, Tetra-PEG gels have been prepared by the cross-end-coupling of A- and B-type Tetra-PEG prepolymers in a 1:1 ratio, forming "symmetric gels", to optimize the uniformity of the network structure and the mechanical properties. If the ratio is shifted from symmetry, the network becomes imperfect, resulting in reduced mechanical properties. As a matter of fact, the compression modulus and the strain and stress at break were highest in the 1:1 combination and were decreased when deviating from the stoichiometric ratio.[28] Sakai et al. intentionally varied this ratio and obtained sol–gel transition curves as a function of polymer concentration (volume fraction, ϕ_0) and the ratio r. This is a site-bond percolation problem, as discussed by Coniglio et al.[62] They treated the percolation problem with two parameters: site and bond probabilities. Figure 7a,b schematically shows that all sites are occupied by "monomer", i.e., a bulk system without solvent. Here, the monomer is capable of bonding to a neighboring monomer either chemically or physically. Figure 7a,b shows the behavior below the percolation threshold and at or above the percolation threshold, respectively. This type of percolation is called "bond" percolation. On the other hand, in Figure 7c, some sites are occupied by "solvent" molecules, which are not capable of bonding. As a result, the percolation is governed not only by the "bond" but also by the active "site" (i.e., monomer). A large amount of solvent is present in polymer gels. Hence, the "site" corresponds to the fraction of the occupied site, i.e., the monomer concentration, and the "bond" is proportional to the cross-linker concentration. Examples of site–bond percolation can be found in polymer gels undergoing physical gelation[63] and chemical gelation.[64] In the Tetra-PEG system, the "site" and "bond" can be either A or B, i.e., a symmetric site–bond percolation where the two components are identical in architecture, functionality, and reactivity but differ in composition. Sakai et al. employed a set of TAPEG and TNPEG prepolymers with a molecular weight of 20 kg mol^{-1}. Figure 8 shows the phase diagram[65] determined by a series of viscoelastic measurements, i.e., the method proposed by Winter and Chambon.[66] The scaling exponent Δ, characterized by $G' \sim G'' \sim \omega^{\Delta}$, was obtained to be 0.69.[65] The

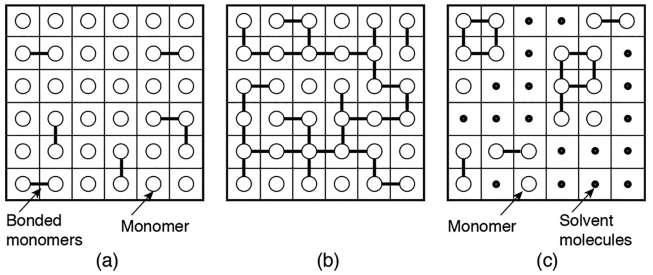

Figure 7. Schematic model of site–bond percolation. Panels (a) and (b) show that all sites are occupied by monomers (open circles) and correspond to the behavior below and at the percolation threshold (bond percolation), respectively. In panel (c), on the other hand, solvent molecules occupy some sites and behave as non-active sites. Hence, percolation is governed not only by the "bonds" but also by the "sites" (site-bond percolation). Reproduced with permission from ref 62. Copyright 1979 The American Physical Society.

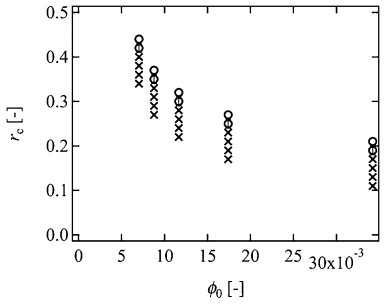

Figure 8. Phase diagram of asymmetric Tetra-PEG systems (circle, sol; cross, gel) Determined by viscoelastic measurements. Reproduced with permission from ref 65. Copyright 2016 The Society of Polymer Science, Japan.

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range of Δ is known to be $2/3 \leq \Delta \leq 1$.[67] The obtained value corresponds to the Rouse dynamics (the limit of complete hydrodynamic screening), although the Tetra-PEG system seems to be the other extreme considering the volume fraction. A similar exponent was also obtained by Adibnia and Hill for a gradually cross-linking polyacrylamide solution.[68] Note that the lowest volume fraction, ϕ_{0c}, for gelation at $r = 0.5$ (the symmetric case) is much smaller than the so-called chain overlap polymer volume fraction (ϕ^*) and was about $\phi^*/6$. It is interesting to note that a polymer gel can be prepared at a concentration far below ϕ^*, where a fibrillar network is formed, similar to a physical gel composed of low-molecular-weight gelators.[69,70]

Li et al. investigated the structures of Tetra-PEG critical clusters.[43] Here, the reactants were changed from TAPEG and TNPEG to maleimide-terminated Tetra-PEG (MA-PEG; r) and thiol-terminated Tetra-PEG (TH-PEG; $1 - r$), where r is the fraction of MA-PEG. This system does not undergo hydrolysis (discussed in Figure 3b), and hence, the sol−gel transition can be determined more precisely than when TAPEG and TNPEG are used (Figure 3). Figure 9 schematically shows

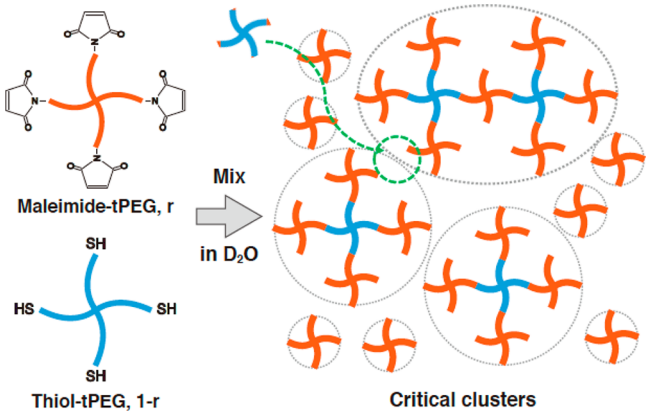

Figure 9. Illustration of the synthesis of critical clusters by mixing two different types of tetra-armed PEG prepolymers with mutual reactive end groups (maleimide-Tetra-PEG and thiol-Tetra-PEG). The cluster can percolate by adding a "blue" unit (shown as a blue cross) to the critical cluster system (shown as a dashed green line and circle). Reproduced with permission from ref 43. Copyright 2017 American Chemical Society.

a critical cluster system just below the gelation threshold. This figure indicates that the system would percolate by adding a "blue" unit (as shown with a blue cross) to the critical cluster system (as shown with a dashed green line and circle). Figure 10 shows the schematic illustration of the sol−gel phase diagram and the sample recipe for the SANS experiments. The solid curve represents the sol−gel transition curve, and the closed red circles show the critical clusters prepared based on the sol−gel transition curve. The open circles show polymer clusters that are diluted from the as-prepared polymer clusters. Figure 11 shows the SANS results for the samples along the sol−gel transition curve. Here, the SANS curve can be divided to a low-q region (cluster region) and a high-q region (prepolymer region), as shown by the structures. Here, $I(q)$ is the scattering intensity, q is the magnitude of the scattering vector, and ϕ is the polymer volume fraction. By analyzing the SANS data along the sol−gel transition curve and along the dilution line (see Figure 10), the following conclusion was obtained: The fractal dimension of the critical clusters was estimated to be approximately 2.0, irrespective of the preparation conditions of the critical clusters. The fractal dimension, D, is defined as $M \sim R^D$, where M and R are the mass and the characteristic size of the system, respectively. As shown in Figure 11, the mass of the system (a four-arm polymer chain) in the prepolymer region is proportional to R^D, and the obtained value of the fractal dimension was $D = 1.8 \approx 5/3$, i.e., the fractal dimension of polymer chains in a good solvent. On the other hand, in the cluster region, the interpolymer chains are screened, and the fractal dimension is recovered for the screened polymer chains ($D = 2$). The estimated fractal dimension, $D = 2.1$, agrees with the prediction of the 3D percolation model for swollen branched polymer chains ($D = 2.0$)[71] and with experimentally obtained values ($D = 1.98-2.06$).[72] The Fisher exponent,[71−73] on the other hand, is a measure of the polydispersity of the cluster size, and the value is dependent on the model, e.g., 5/2 (tree model) or 2.20 (percolation). Experimentally, this value was estimated to be 1.90−2.25,[72] which was found to depend on the preparation conditions of the critical clusters. Li et al. clearly showed that the fractal structure of the critical clusters is universal, irrespective of the synthetic conditions, while the size distribution of critical clusters can be tuned. For further details, see the work of Li et al.[43]

Fast-Forming Gel with Ultra-low Osmotic Modulus. One possible biological application of gels is in ophthalmology, such as artificial corneas, vitreous bodies, and lenses. In the current treatment of retinal detachment, a patient must be hospitalized for several days to cure retinal damage, which is painful to the patient. If an artificial vitreous body can be implanted in the body without the need for a surgical procedure, via syringe for example, the damage to the patient would be minimal. In this case, the implant must be in liquid form before application by syringe but in a gel state after application. Therefore, quick gelation is required for the gel to be implanted. Another requirement is that the osmotic pressure of the implanted gel must be low enough to be compatible with surrounding tissue. Otherwise, the implanted gel swells in the body (or in the eyeball), causing serious damage.[74] In fact, there is a trade-off between these two requirements. The lower the osmotic pressure, the longer it takes for gelation. For example, more than 7 h is required for a gel with polymer concentration of 6.0 g/L.[75]

Recently, Sakai and co-workers solved this problem using a two-step gelation method. As shown in Figure 12, they prepared a set of critical clusters called "oligo-Tetra-PEGs" by mixing Tetra-PEG-A and Tetra-PEG-B in off-stoichiometric ratios: one rich in A, and another rich in B. Here, the polymer concentrations and the off-stoichiometric ratios are set to form critical clusters just below the gelation threshold (see Figure 8). The set of critical clusters, i.e., a pair of oligo-Tetra-PEGs, was then mixed with vigorous stirring. In this case, Tetra-PEG gels with very low osmotic pressure were readily formed in a few minutes. The following relation should be noted: swelling pressure = osmotic pressure − elastic pressure. This means that the osmotic pressure always exists whenever polymer chains are in the body, while elastic pressure disappears by dissociation. They applied this method for the retinal detachment treatment of a rabbit with a great success (see demo movie: https://www.youtube.com/watch?v=7EzWR5GD_XI). This method opens a wide range of applications of polymer gels to medical treatment. This is one example in which gels become BioMatter, i.e., an artificial vitreous body with appropriate

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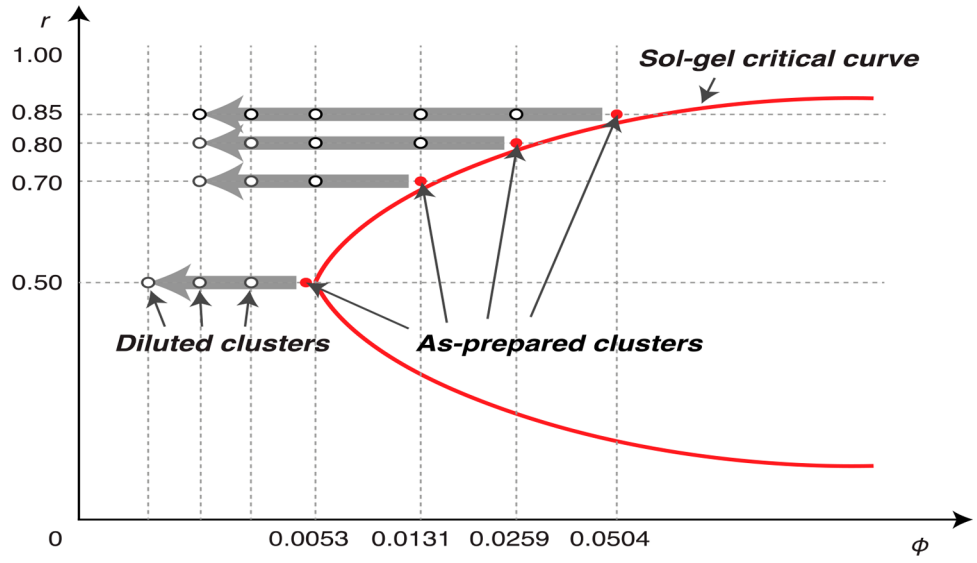

Figure 10. Schematic representation of the sol−gel phase diagram and the sample ratio in the SANS experiments. Reproduced with permission from ref 43. Copyright 2017 American Chemical Society.

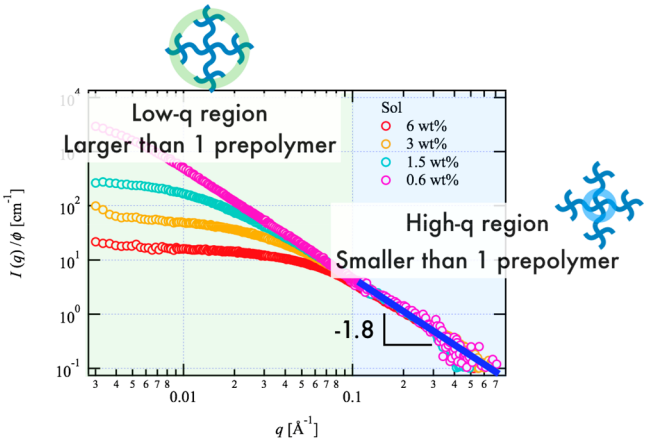

Figure 11. SANS results of the samples along the sol−gel transition curve: (left) low-q region (cluster region) and (right) high-q region (prepolymer region). Reproduced with permission from ref 43. Copyright 2017 American Chemical Society.

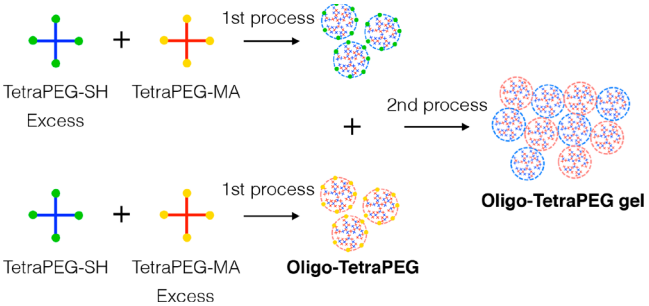

Figure 12. Preparation scheme of fast-forming oligo-Tetra-PEG gels via oligo-Tetra-PEG clusters. Reproduced with permission from ref 75. Copyright 2017 Macmillan Publishers Limited.

stiffness and extremely low swelling pressure compatible with living tissue.[75]

4. CONCLUDING REMARKS

One of the ultimate goals in the long history of the science and technology of hydrogels is their biomedical application. A number of gels have been proposed, such as pH-responsive and thermoresponsive gels, drug-delivery systems, sensors and actuators, artificial muscles and tendons, and so on. Most of these gels have advanced properties in vitro but not in vivo. Once implanted in the body, their properties degrade, or they can even become harmful. This means that these gels cannot be used in vivo. In this Review, we demonstrated how to overcome existing problems for biomedical applications of gels. Starting from a biocompatible polymer, i.e., poly(ethylene glycol), a quick but precise and near-perfect gelation method, i.e., cross-end-coupling of complementary Tetra-PEG prepolymers, is proposed. These Tetra-PEG gels have led to a paradigm shift. Now, various types of gels have been prepared, including defect-free gels, tough gels, regular networks, and so on. We then examined biomedical applications of Tetra-PEG gels, such as non-swellable gels, fuse-linked gels, and fast-forming gels with ultra-low osmotic pressures. It should be noted that this research was not achieved through the close collaboration of bioengineers and polymer physicists. We propose calling these gels "BioMatter", which is a term coined by combining biology and matter but intentionally means biocompatible/biofriendly materials. Further developments are in progress.

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Notes

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