Multidomain Hybrid Hydrogels: Spatially Resolved Photopatterned Synthetic Nanomaterials Combining Polymer and Low-Molecular-Weight Gelators**

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Abstract: A simple approach to a patterned multidomain gel is reported, combining a pH-responsive low-molecular-weight gelator (LMWG) and a photoinducible polymer gelator (PG). Using SEM (scanning electron microscopy), NMR spectroscopy, and CD, we demonstrate that self-assembly of the LMWG network occurs in the presence of the PG network, but that the PG has an influence on LMWG assembly kinetics and morphology. The application of a mask during photoirradiation allows patterning of the PG network; we define the resulting system as a "multidomain gel"—one domain consists of a LMWG, whereas the patterned region contains both LMWG and PG networks. The different domains have different properties with regard to diffusion of small molecules, and both gelator networks can control diffusion rates to give systems capable of controlled release. Such materials may have future applications in multikinetic control of drug release, or as patterned scaffolds for directed tissue engineering.

ydrogels are responsive soft materials with potential applications ranging from tissue engineering to controlled drug release. Such materials typically fall into two groups— 1) polymer gels (PGs)^[1] or 2) low-molecular-weight supramolecular gels (LMWGs).^[2] Each type of gelator has its own advantages—polymer gels usually form relatively robust network materials often with covalent chemical crosslinking, whereas self-assembled LMWGs are held together by noncovalent interactions and are therefore typically weaker, but more responsive. In principle, harnessing the potential of both types of gelator using a multicomponent approach can yield multifunctional gels.

Controlling the internal spatial structuring of a gel would have great potential for the development of hybrid materials with enhanced activity.^[3] One route to achieve this goal would be to use gels containing more than one component, where the individual gelation systems could be addressed individually in a spatially resolved manner. We became interested in the application of combined polymer and low-molecular-

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Angew. Chem. Int. Ed. 2014, 53, 1-6

weight gelators, which can be addressed by different stimuli. The combination of PGs and LMWGs has only recently begun to be employed. PGs used in such systems have included naturally occurring gelation systems, such as agarose,^[4] calcium alginate,^[5] and konjac glucomannan.^[6] We recently investigated the assembly of 1,3;2,4-dibenzylidene-D-sorbitol dicarboxylic acid (DBS-CO₂H), a pH-dependent gelator, in the presence and absence of agarose.^[4c] We found that although the kinetics of assembly of DBS-CO₂H were slightly changed in the presence of the PG, the hybrid material could be considered a self-sorting multicomponent gel. The LMWG could be assembled/disassembled inside the stable PG network by pH switching, demonstrating how hybrid gels can have the potential to be both responsive and robust.

To our knowledge, there are no current examples of a synthetic, covalently crosslinked polymer gelator being used in hybrid hydrogels. We therefore decided to test the feasibility of such a material by combining DBS-CO₂H with poly(ethylene glycol) dimethacrylate (PEGDM; Figure 1).



Figure 1. Gelator structures—low-molecular-weight gelator DBS-CO $_2$ H and polymer gelator PEGDM.

PEG-based hydrogels (PEG = poly(ethylene glycol)) are widely-used in biomedical applications,^[1a-c,7] such as drug delivery and tissue engineering. PEG is covalently crosslinked to form a gelator network, usually by UV photopolymerization of PEG acrylates, such as PEG methacrylate (PEGMA), PEG diacrylate (PEGDA), or PEG dimethacrylate (PEGDM). Furthermore, we reasoned that such systems could be potentially photoaddressable, and give hybrid multicomponent gels with spatial resolution.

PEGDM was synthesized by stirring PEG (M_n = 8000 gmol⁻¹) with methacrylic anhydride (2.2 equivalents) in the presence of triethylamine for 4 days, followed by the addition of ether to precipitate PEGDM.^[8] PEGDM hydrogels were prepared by dissolving PEGDM at varying percentages of weight/volume (wt/vol) in a solution of 2-hydroxy-4'-(2-hydroxyethoxy)-2-methylpropiophenone as photoinitiator

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(PI) in water (0.05% wt/vol, 1 mL).^[9] The solutions were cured with a long wavelength UV light source ($\lambda = 315-405 \text{ nm}$, PI activation at $\lambda = 365 \text{ nm}$)^[10] for 10 minutes to obtain optically transparent hydrogels by radical photopolymerization. The minimum gelation concentration (MGC) was found to be approximately 5% wt/vol.

The preparation of DBS-CO₂H hydrogels has been reported.^[4c] In brief, DBS-CO₂H was dissolved by basification of an aqueous suspension (pH \approx 11), followed by the addition of glucono- δ -lactone (GdL), which slowly hydrolyzed to yield gluconic acid, lowering the pH value to 3–4 (depending on the amount of GdL used) and causing homogeneous, translucent gels to form.^[11] As such, these two gels have orthogonal methods of preparation—UV-initiated photopolymerization and pH change—which makes it possible to examine each gelator and network individually at the molecular and nanoscales and potentially address the orthogonal gel networks individually.

Hybrid gels were prepared by adding DBS-CO₂H (0.05% wt/vol) to a PEGDM/PI solution (5% wt/vol) prepared as described above, followed by the addition of NaOH (0.5 M in 10 μ L aliquots) to dissolve DBS-CO₂H. GdL (6–8 mg) was added, immediately followed by UV curing for 10 minutes to obtain a clear hydrogel. This mixture was then left overnight for gelation of DBS-CO₂H to occur. The next day, the gel had gone from clear to translucent, suggesting the formation of the LMWG network.

We then investigated the hybrid gel in detail. Xerogels were imaged using scanning electron microscopy (SEM, Figure 2). Samples were prepared by freeze-drying in liquid nitrogen to stabilize the network, followed by lyophilizing overnight. DBS-CO₂H had quite rigid and well-defined fibers (Figure 2 a), whilst the xerogel of a PEGDM hydrogel had a less well-defined structure, with a mix of film, ribbon, and fibrous morphologies being observed (Figure 2 b). The xerogel of the hybrid material showed some characteristics of both gels—importantly, it was evident that the well-defined DBS-CO₂H fiber morphologies could still clearly be observed, though embedded/coated in the PEGDM network, which appears to lead to a slightly less dense/branched DBS-CO₂H network (Figure 2 c).

The kinetics of assembly of DBS-CO₂H in the presence of PEGDM were studied using NMR spectroscopic methods, which are a powerful way of examining gel dynamics at a molecular level.^[12] A solid-like gel network is immobile on the NMR timescale and thus NMR invisible; only molecules in the liquid-like phase are NMR visible. We monitored the evolution of the NMR spectrum over time after addition of GdL, and compared the results for DBS-CO₂H in the absence and presence of PEGDM (Figure 3a). For both systems, DBS-CO₂H gradually becomes immobile as it assembles to form a gelator network. There was a significant decrease in the rate of DBS-CO₂H immobilization in the presence of PEGDM, indicating that the PG network has some effect on the kinetics of DBS-CO₂H assembly.



Figure 2. SEM images of xerogels formed by: DBS-CO₂H (a), PEGDM (b), and DBS-CO₂H and PEGDM (c). Scale bars = 1 μ m.

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Figure 3. a) Kinetics of formation of DBS-CO₂H network in the absence (blue) and presence (red) of PEGDM, as monitored by NMR spectroscopy. b) Kinetics of evolution of CD spectra over time, monitoring ellipticity at $\lambda = 260$ nm, after addition of GdL (34 mM): DBS-CO₂H (0.02% wt/vol, blue trace); DBS-CO₂H/PEGDM (0.02%/ 0.5% wt/vol, red trace).

Angew. Chem. Int. Ed. 2014, 53, 1-6

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We then applied the Avrami kinetic model [Eq. (1)]^[13] to the data (see Supporting Information, section 6 for more details), to determine the Avrami exponent, n, which reflects the dimensionality of "crystal" (or fiber) growth:^[14]

$$1 - X(t) = \exp(-\mathbf{K} t^n) \tag{1}$$

The Avrami exponent for DBS-CO₂H in the absence of PEGDM was 1.61, whilst in the presence of PEGDM it was 1.45, indicating less branching or 2D growth in the presence of the PG. From this result, we surmise that whilst DBS-CO₂H is able to assemble into its own nanofiber network, it is affected by the presence of PEGDM. This is most likely as a result of the increased viscosity of the liquid-like phase associated with the PG—increased viscosity limits the rate of diffusion of the LMWG and its assembly into fibers. This has been noted in other hybrid gels,^[5a,6] and may also explain the network observed by SEM, with the PG limiting fiber branching.

We then probed the initial stages of LMWG fiber growth by CD spectroscopy. The aromatic rings of DBS-CO₂H provide a useful chromophoric reference point at $\lambda =$ 260 nm; by recording the evolution of these bands over 2 hours after the addition of GdL, further insight into fiber assembly could be gained (Figure 3b). CD spectroscopy was performed below the gelation threshold of both DBS-CO₂H (0.02 % wt/vol) and PEGDM (0.5 % wt/vol)—therefore we do not detect the formation of a full sample-spanning network, just nanofiber assembly.

In both systems there was an induction phase, followed by a slight increase in CD ellipticity, after which the emergence of the CD band associated with DBS-CO₂H nanofibers was detected. The induction phase for DBS-CO₂H in the presence of PEGDM was significantly longer, in keeping with the idea that increased viscosity of the liquid-like phase limits diffusion and initial nucleation. The timescale of rapid increase in ellipticity for both systems is roughly the same (ca. 20 minutes), though the hybrid system is at a greater ellipticity after 2 hours (ca. -85 versus -50 mdeg). However, on further standing (for up to 5 hours), the ellipticity of DBS- CO_2H decreased to circa -40 mdeg for the LMWG by itself. and -60 mdeg for the hybrid hydrogel-this shows further slow evolution of the nanofibers (see Supporting Information). We suggest that these systems initially assemble into a metastable state^[15] which then reorganizes slowly over time-the presence of the PG clearly affects the kinetics of this process.

After investigating the hybrid gel at molecular and nanoscales, we became interested in its macroscopic materials properties. In particular, we wanted to see if it was possible to obtain spatial resolution within our multicomponent gel system. We hoped to use photoirradiation to pattern regions of hybrid gel in a bulk gel sample. We reasoned that the properties of the material may be modified, depending on whether one or two gel networks were present in a specific region: for example, the rates of diffusion within nonhybrid (single network) and hybrid (dual network) gels.

To form such spatially resolved gels, a solution of both gelators (10 mL), plus PI and GdL, was added to a mold. A Y-shaped mask (Y for York) was then applied over the top

and the mixture was cured under UV light for 20 minutes; only in those areas exposed to UV light (specifically, the Yshaped region in the center) did a PEGDM (PG) gel form. The molds were then left overnight to allow the DBS- CO_2H (LMWG) network to continue assembling as slow acidification progresses (Figure 4). After this time, the whole mold



Figure 4. A) Patterned multidomain gel consisting of nonhybrid singlenetwork region (less transparent) and hybrid dual-network Y-shaped region (more transparent). B) The nonhybrid domain is easily deformed, whilst C) the hybrid region can be removed intact. D) Diffusion of DR80 dye from left edge after approximately 60 seconds. E) Diffusion of dye after circa 3 hours. F) Diffusion of dye after circa 24 hours: the nonhybrid region is nearly completely stained, whilst there is only minimal diffusion into the hybrid region (center).

was filled with gel, but two regions were still distinctly visible, showing a Y-shaped spatially patterned gel (Figure 4A). The hybrid region (center) was more transparent, which may be as a result of the LMWG fibers being thinner or less clustered in this region, leading to greater optical transparency. The hybrid region was also noticeably stronger—the nonhybrid region could easily be broken (Figure 4B), but the hybrid region could be removed intact (Figure 4C). This shows that the presence of a PG network can significantly enhance the mechanical stability of LMWG-derived gels.^[4-6] We refer to this patterned soft material as a multidomain gel.

A solution of Direct Red 80 dye ($1 \text{ mgmL}^{-1} \text{ H}_2\text{O}$) was then applied to the edge of the gel (Figure 4D). Rapid diffusion of the dye was seen in the nonhybrid region (Figure 4E), and after 24 h the whole single-network gel domain was stained red (Figure 4F). In contrast, the dye barely diffused into the hybrid domain, even after 2 days. This is likely because the dense network of crosslinked PEGDM fibers in the hybrid region prevents easy diffusion of the relatively large dye molecules.

To understand diffusion in these multidomain gels in more detail, and to investigate the potential of these hybrid systems

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for controlled release, we encapsulated three different dyes— Direct Red 80 (DR80), malachite green (MG), and methylene blue (MB)—within a gel sample and then examined their release. PEGDM and hybrid gels containing each of the dyes were prepared as described above, substituting water for a solution of the selected dye (0.1 mgmL^{-1}). Cylinders of the gels (0.5 mL) were submerged in buffer solution (30 mL, pH 7, phosphate) and the release of the dyes over time was monitored by UV/Vis absorption spectroscopy (Figure 5).



Figure 5. Structures of the dyes: a) Direct Red 80 (DR80), b) malachite green oxalate (MG), and c) methylene blue chloride (MB). d) Spectrum showing the percentages of dye released from both PEGDM and hybrid gels in pH 7 buffer solution.

For DR80, no release of dye, either from the PG or the hybrid system, was detected. This is in agreement with the photopatterning experiment outlined above in which this dye could not diffuse into the photopatterned hybrid domain. We propose that the large size of DR80 physically hinders its diffusion within the PG gel network.

For MG, the dye was released from the gel network over a 24 hour timescale, with up to 30% being released. This suggests that this smaller dye is able to diffuse out of the PG network, although some dye clearly remains entrapped, perhaps locked in poorly accessible pores within this relatively dense network. Interestingly, the PG and hybrid system both released MG at exactly the same rate, indicating that the presence of the LMWG network has no influence on diffusion and that the PG network is dominating the behavior.

Interestingly, however, MB showed very different diffusion depending on whether the gel was the PG or the hybrid material. For the hybrid gel, 35% was released over 24 hours, whereas for PG alone as much as 55% was released. This indicates that for MB, the presence of the LMWG has a significant effect, hindering dye diffusion. For the PG alone, more of this small dye is released than either of the larger dyes. The effect of the LMWG cannot therefore be a consequence of sterics. As such, we propose that there are specific interactions between MB and the self-assembled LMWG network. Indeed, it has been established that acid and/or hydrazide-functionalized LMWGs can form specific interactions with MB.^[16] A simple adsorption study comparing the percentage dye uptake of MB or MG by a DBS-CO₂H gel showed preferential adsorption of MB (see the Supporting Information), supportive of the view that there are specific interactions between MB and the DBS-CO₂H gel nanofibers. A comparison of transmission electron microscopy (TEM) images of DBS-CO₂H gels with and without MB showed no significant difference in fiber structure, suggesting that acidbase interactions at the fiber periphery are the main cause of dye adsorption (intercalation would likely cause a significant change in fiber morphology).^[16a,b]

Importantly, these studies clearly illustrate how both PG and LMWG networks can have a profound influence on controlled release from these hybrid systems either through steric effects (in the case of PG and larger dyes) or specific interactions between gel nanofibers and dyes (in the case of LMWG and the dye MB).

In conclusion, we have demonstrated the first combination of a LMWG (DBS- CO_2H) with a synthetic PG (PEGDM). The hybrid gel appears by SEM to contain a mixture of PEGDM and DBS- CO_2H nanostructures, supported by circular dichroism which indicates the presence of chiral nanostructures that can be assigned to DBS- CO_2H . Importantly, different regions can be spatially patterned by photoirradiation, controlling whether one or two networks are present and leading to differences in materials behavior and diffusion. We have also demonstrated that these hybrid gels have the potential to be used for multi-mechanism controlled release. The presence of both PG and LMWG networks within the hybrid gel can exert an influence on the properties of the material—specifically diffusion within the network.

We believe hybrid LWMG/PG gels have significant potential for high-technology applications. For example, by writing patterns into multidomain materials it should be possible to generate drug-delivery gels which can exhibit differential kinetics of drug release from different regions of the gel to achieve both burst and sustained release from a single system. Furthermore, it may be possible to use this approach to write patterns into tissue engineering materials to encourage differential cell growth, with laser irradiation providing more complex photopatterns with significantly greater spatial definition. Research into applications for this multidomain hybrid gel technology is currently in progress.

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Communications

Multidomain Gels

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Multidomain Hybrid Hydrogels: Spatially Resolved Photopatterned Synthetic Nanomaterials Combining Polymer and Low-Molecular-Weight Gelators



The best of both worlds: Forming polymer gel networks embedded within a lowmolecular-weight gel matrix using photoirradiation allows the generation of multicomponent nanoscale soft materials. The different gel domains have different properties, for example, with regard to the diffusion of small molecules, such as dyes, depending on which nanoscale networks they contain (see picture).

6 www.angewandte.org

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