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**Article:**

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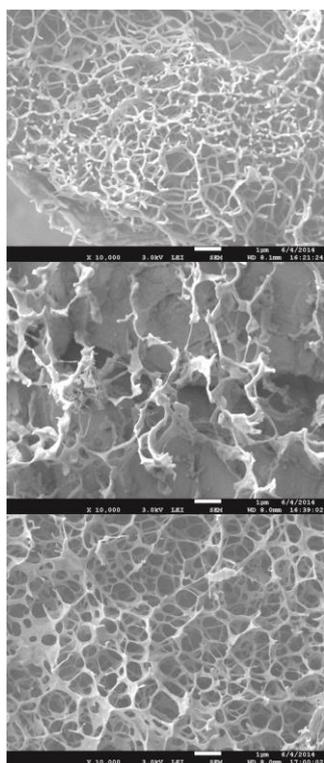
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source (315–405 nm, PI activation at 365 nm)<sup>[10]</sup> for 10 minutes to obtain optically transparent hydrogels by radical photopolymerisation. The minimum gelation concentration (MGC) was found to be *ca.* 5% wt/vol.

The preparation of DBS-CO<sub>2</sub>H hydrogels has been previously described by us;<sup>[4c]</sup> in brief, DBS-CO<sub>2</sub>H is dissolved by basification of an aqueous suspension (pH ≈ 11), followed by the addition of glucono-δ-lactone (GdL), which slowly hydrolyses to yield gluconic acid, lowering the pH to 3–4 (dependent on amount of GdL used) and causing homogeneous, translucent gels to form.<sup>[11]</sup> As such, these two gels have orthogonal methods of preparation – UV initiated photopolymerisation and pH change – which makes it possible to examine each gelator and network individually at the molecular and nano scales and potentially address the orthogonal gel networks individually.

Hybrid gels were prepared by adding DBS-CO<sub>2</sub>H (0.05% wt/vol) to a PEGDM/PI solution (5% wt/vol) prepared as described above, followed by addition of NaOH (0.5 M in 10 μL aliquots) to dissolve DBS-CO<sub>2</sub>H. 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-CO<sub>2</sub>H to occur. The next day, the gel had gone from clear to translucent, suggesting the formation of the LMWG network.



**Figure 2.** SEM images of xerogels formed by: (top) DBS-CO<sub>2</sub>H; (middle) PEGDM; (bottom) DBS-CO<sub>2</sub>H and PEGDM. Scale bars = 1 μm.

We then investigated the hybrid gel in detail. Xerogels were imaged using scanning electron microscopy (SEM) (Fig. 2); samples were prepared by freeze-drying in liquid nitrogen in order to stabilise the network, followed by lyophilising overnight. DBS-CO<sub>2</sub>H had quite rigid and well-defined fibres (Fig 2a), whilst the xerogel of a PEGDM hydrogel had a less well-defined structure, with a mix of film, ribbon and fibrous morphologies being observed (Fig. 2b). The xerogel of the hybrid material showed some characteristics of both gels – importantly, it was evident that the well-defined DBS-CO<sub>2</sub>H fibre morphologies could still clearly be observed, though embedded/coated in the PEGDM network, which

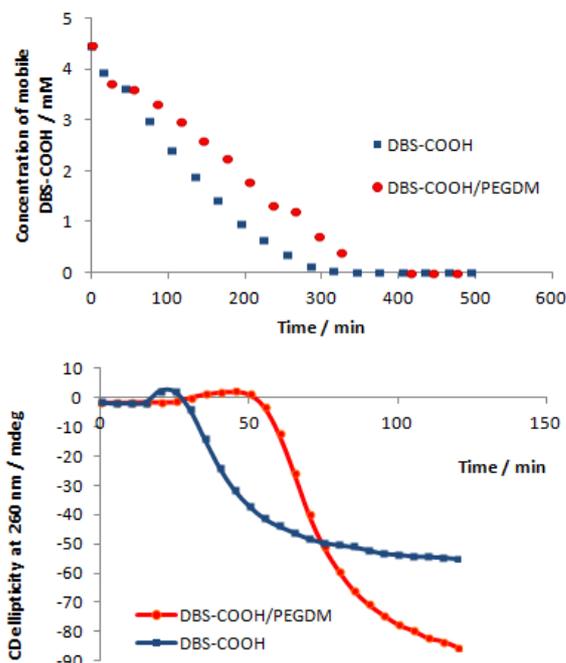
appears to lead to a slightly less dense/branched DBS-CO<sub>2</sub>H network (Fig. 2c).

The kinetics of assembly of DBS-CO<sub>2</sub>H in the presence of PEGDM were studied using NMR methods, which are a powerful way of examining gel dynamics at a molecular level.<sup>[12]</sup> A solid-like gel network is immobile on the NMR timescale, and hence 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-CO<sub>2</sub>H in the absence and presence of PEGDM (Fig. 3). For both systems, DBS-CO<sub>2</sub>H gradually becomes immobile as it assembles into a gelator network. There was a significant decrease in the rate of DBS-CO<sub>2</sub>H immobilisation in the presence of PEGDM, indicating that the PG network has some effect on the kinetics of DBS-CO<sub>2</sub>H assembly.

We then applied Avrami's kinetic model (equation 1)<sup>[13]</sup> to the data, to determine the Avrami exponent, *n*, which reflects the dimensionality of 'crystal' (or fibre) growth (see electronic supplementary information (ESI), section 6 for more detail).<sup>[14]</sup>

$$1 - X(t) = \exp(-Kt^n) \quad (1)$$

The Avrami exponent for DBS-CO<sub>2</sub>H 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, we surmise that whilst DBS-CO<sub>2</sub>H is able to assemble into its own nanofibre network, it is affected by the presence of PEGDM. This is most likely due to 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 fibres. This has been noted in other hybrid gels,<sup>[5a,6]</sup> and may also explain the network observed by SEM, with the PG limiting fibre branching.



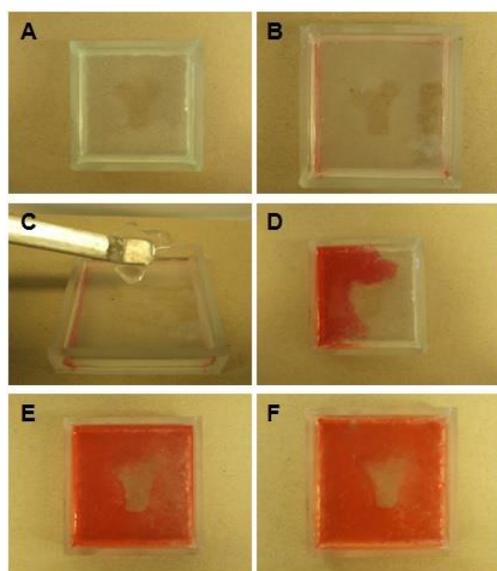
**Figure 3.** Top: Kinetics of formation of DBS-CO<sub>2</sub>H network in absence (blue) and presence (red) of PEGDM, as monitored by NMR spectroscopy. Bottom: Kinetics of evolution of CD spectra over time, monitoring ellipticity at 260 nm, after addition of GdL (34 mM): (blue) DBS-CO<sub>2</sub>H (0.02% wt/vol); (red) DBS-CO<sub>2</sub>H/PEGDM (0.02%/0.5% wt/vol).

We then probed the initial stages of LMWG fibre growth by CD spectroscopy. The aromatic rings of DBS-CO<sub>2</sub>H provide a useful chromophoric handle at *ca.* 260 nm; by recording the evolution of these bands over 2 hours after addition of GdL, further insight into fibre assembly could be gained (Fig 3). CD spectroscopy was performed below the gelation threshold of both DBS-CO<sub>2</sub>H (0.02%

wt/vol) and PEGDM (0.5% wt/vol) – therefore we do not observe the formation of a full sample-spanning network, just nanofibre 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-CO<sub>2</sub>H nanofibres was observed. The induction phase for DBS-CO<sub>2</sub>H 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 min), though the hybrid system is at a greater ellipticity after 2 hours (*ca.* -85 vs. *ca.* -50 mdeg). However, on further standing (for up to 5 hours), the ellipticity of DBS-CO<sub>2</sub>H decreased to *ca.* -40 mdeg for the LMWG by itself, and *ca.* -60 for the hybrid hydrogel (see ESI) – this shows further slow evolution of the nanofibres. We suggest that these systems initially assemble into a metastable state<sup>[15]</sup> which then reorganise slowly over time – the presence of the PG clearly affects the kinetics of this process.

After investigating the hybrid gel at molecular and nano scales, we became interested in its macroscopic materials properties. In particular, we wanted to see if it was possible to obtain spatial resolution within our multi-component gel system. We hoped to use photo-irradiation 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 non-hybrid (single network) and hybrid (dual network) gels.



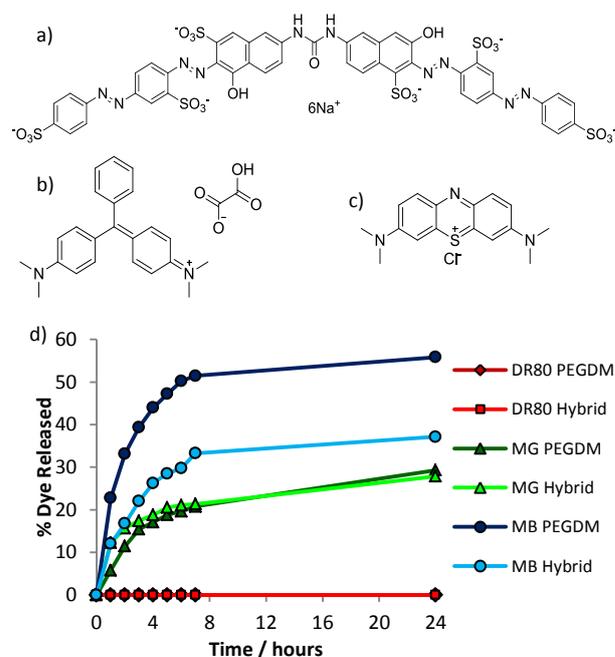
**Figure 4.** (A) Patterned multi-domain gel consisting of non-hybrid single-network region (more translucent) and hybrid dual-network Y-shaped region (less translucent). (B) The non-hybrid domain is easily deformed, whilst (C) the hybrid region can be removed intact. (D) Diffusion of DR80 dye from left edge at *ca.* 60 s. (E) Diffusion of dye at *ca.* 3 h. (F) Diffusion of dye at *ca.* 24 h – non-hybrid region is nearly completely stained, whilst there is only minimal diffusion into hybrid region.

To form such spatially resolved gels, a solution of both gelators (10 ml), plus PI and GdL, was added to a mould, a Y-shaped mask (Y for ‘York’) was then applied over the top and the mix was cured under UV light for 20 minutes; only in those areas exposed to UV light did a PEGDM (PG) gel form. The moulds were then left overnight to allow the DBS-CO<sub>2</sub>H (LMWG) network to continue assembling as slow acidification progresses (Fig. 4). After this time, the whole mould was filled with gel, but two regions were still distinctly visible (Fig. 4A showing a ‘Y’ spatially-patterned gel) – the hybrid region was less translucent (this may be due to the LMWG fibres being thinner or less clustered in this region, leading

to greater optical transparency). The hybrid region was also noticeably stronger – the non-hybrid region could easily be broken (Fig. 4B), but the hybrid region could be removed intact (Fig. 4C). This shows that the presence of a PG network can significantly enhance the mechanical stability of LMWG-derived gels.<sup>[4-6]</sup> We refer to this patterned soft material as a multi-domain gel.

A solution of Direct Red 80 dye (1 mg/ml H<sub>2</sub>O) was then applied to the edge of the gel (Fig. 4D). Rapid diffusion of the dye was seen in the non-hybrid region (Fig. 4E), and after 24 hours the whole single network gel domain was stained red (Fig. 4F). In contrast, the dye barely diffused into the hybrid domain, even after 2 days. This is likely due to the dense network of crosslinked PEGDM fibres in the hybrid region preventing easy diffusion of the relatively large dye molecules.

To understand diffusion in these multi-domain gels in more detail, and to investigate the potential of these hybrid systems for controlled release, we encapsulated three different dyes – Direct Red 80 (DR80), malachite green (MG) and methylene blue (MB) – within a gel sample, then examined their release. PEGDM and hybrid gels contain each of the dyes were prepared as per the methods described above, substituting water for a 0.1 mg ml<sup>-1</sup> solution of the selected dye. Cylinders of the gels (0.5 ml) were submerged in 30 ml of buffer solution (pH 7, phosphate) and the release of the dyes over time monitored by UV-vis spectroscopy (Fig. 5).



**Figure 5.** Structures of dyes (a) Direct Red 80, (b) malachite green oxalate, and (c) methylene blue chloride. A comparison of percentages of dye released from both PEGDM and hybrid gels in pH 7 buffer solution is shown in (d).

For DR80, no release of dye either from the PG or the hybrid system was observed. This is in line with the photo-patterning experiment outlined above in which this dye could not diffuse into the photo-patterned 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 both released MG at exactly the same rate, indicating that the presence of the LMWG network has no impact on diffusion and that the PG network is dominating the behaviour.

Interestingly, however, MB showed very different diffusion depending on whether the gel was PG or hybrid. 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 impact, 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 is known in the literature that acid and/or hydrazide functionalised LMWGs can form specific interactions with MB.<sup>[16]</sup> A simple adsorption study comparing % dye uptake of MB or MG by a DBS-CO<sub>2</sub>H gel showed preferential adsorption of MB (see ESI) – supportive of the view that there are specific interactions between MB and the DBS-CO<sub>2</sub>H gel nanofibres. A comparison of transmission electron microscopy (TEM) images of DBS-CO<sub>2</sub>H gels with and without MB showed no significant difference in fibre structure, suggesting that acid-base interactions at the fibre periphery are the main cause of dye adsorption (intercalation would likely cause a significant change in fibre morphology).<sup>[16a-b]</sup>

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 nanofibres and dyes (in the case of LMWG and MB).

In conclusion, we have demonstrated the first known combination of a LMWG (DBS-CO<sub>2</sub>H) with a synthetic PG (PEGDM). The hybrid gel appears by SEM to contain a mixture of PEGDM and DBS-CO<sub>2</sub>H nanostructures, supported by CD which indicates the presence of chiral nanostructures that can be assigned to DBS-CO<sub>2</sub>H. Importantly, different regions can be spatially patterned by photo-irradiation, controlling whether one or two networks are present and leading to differences in materials behaviour 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 LMWG/PG gels have significant potential for high-tech applications. For example, by writing patterns into multi-domain materials it should be possible to generate drug delivery gels which can exhibit differential kinetics of drug release from different regions of gel, in order 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 in order to encourage differential cell growth, with laser irradiation providing more complex photo-patterns with significantly greater spatial definition. Research into applications for this multi-domain hybrid gel technology is currently in progress.

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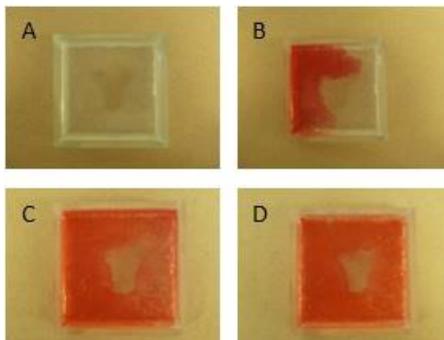
Entry for the Table of Contents (Please choose one layout)

### Multi-Domain Gels

Daniel J. Cornwell, Babatunde O.  
Okesola and David K. Smith\*

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Multi-Domain Hybrid Hydrogels –  
Spatially-Resolved Photo-Patterned Soft  
Nanomaterials Combining Low-  
Molecular-Weight and Synthetic  
Polymer Gelators



The Best of Both Worlds. Forming polymer gel networks using photoirradiation embedded within a low molecular gel matrix allows us to generate multi-component nanoscale soft materials in which the different gel domains have different properties depending on which nanoscale networks they contain.