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Self-Assembling Supramolecular Hybrid Hydrogel Beads

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Abstract: With the goal of imposing shape and structure on supramolecular gels, we combine a low molecular weight gelator (LMWG) with the polymer gelator (PG) calcium alginate in a hybrid hydrogel. By imposing thermal and temporal control of the orthogonal gelation methods, the system either forms an extended interpenetrating network or core-shell structured gel beads – a rare example of a supramolecular gel formulated inside discrete gel spheres. The self-assembled LMWG retains its unique properties within the beads, such as remediating Pd(II) and reducing it *in situ* to yield catalytically-active Pd(0) nanoparticles. A single PdNP-loaded gel bead can catalyse the Suzuki-Miyaura reaction, constituting a simple and easy-to-use reaction dosing form. These unique shaped and structured LMWG-filled gel beads are a versatile platform technology, with great potential in a range of applications.

Supramolecular hydrogels self-assembled from low-molecularweight gelator (LMWG) building blocks in water have seen rapid recent development.^[1] A range of gels has been developed targeting high-tech applications including regenerative medicine, wound healing, pharmaceutical formulation, optoelectronics, energy storage, and environmental remediation.^[2] The physical features of a gel (e.g. stiffness or porosity) as well as the chemical programming inherent within the LMWG scaffold can optimise gels for specific applications. However, in many cases, supramolecular gels suffer from rheological weakness meaning they simply fill the vessel in which they are formed. This can make it challenging to endow self-assembled gels with desired shapes and/or structures, yet the ability to shape and pattern such gels would open up new horizons for LMWGs.^[3] Gels with spatiallyresolved structures could, for example, direct stem cell fate in regenerative medicine,[4] act as vehicles for controlled drug delivery,^[5] or act as patterned conducting gels in integrated soft electronic devices that may ultimately interface with living systems.^[6] A number of strategies have emerged to shape and structure supramolecular gels,^[3] including photopatterning,^[7] 3Dprinting,^[8] electrochemistry^[9] and surface-mediated processes.^[10] Several reports have used controlled diffusion to achieve spatial resolution.^[11] Surprisingly, however, there have been limited reports of supramolecular gel being formulated as spherical particles. Miravet and co-workers reported this by dropwise addition of a DMSO solution of the gelator into an anti-solvent,^[12] while Ulijn and co-workers used microfluidic methods and a waterin-oil emulsion to form gel microspheres.^[13] Spherical nanofibre shells have also been formed via gelator self-assembly at the interface of oil-in-water emulsion microspheres.^[14]

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A key strategy that can enhance the behaviour of LMWGs is to form hybrid gels,^[15] combining them with a polymer gelator (PG) - such systems can, for example, combine the responsiveness of a LMWG with the robustness of a PG network, hence enabling more effective shaping and structuring of the LMWG system.^[3] Alginic acid is a fascinating PG - biocompatible, biodegradable and versatile.^[16] It is a natural poly-saccharide composed of β -Dmannuronic acid and α -L-glucuronic acid units linked through $\beta(1-$ 4) bonds (Fig. 1). Its sodium salt is water-soluble and forms hydrogels when mixed with multivalent cations (e.g. Ca²⁺) by generating ionic interchain bridges. Alginate gel beads can be obtained by dropwise addition of an aqueous alginate solution to CaCl₂.^[17] This is a well-known gel system, explored in schoolslevel education and exploited in pharmaceutical and food sectors.^[18] More complex core-shell alginate beads, in which the interior of the bead is filled with a second component, can also be made.^[19] However, to the best of our knowledge, there are no examples in which a self-assembled LMWG has been incorporated within a polymer microgel bead.



Figure 1. Gelator structures – low molecular weight gelator (LMWG) DBS-CONHNH₂ and polymer gelator (PG) based on alginic acid.

We envisaged a multicomponent gel in which the PG network would effectively act as a spherical mould to constrain LMWG self-assembly. To achieve this, spatial control we decided to combine the alginate PG with 1,3:2,4-di-(4-acylhydrazide)benzylidenesorbitol (DBS-CONHNH₂, Fig. 1), a thermallyresponsive gel, demonstrated to be biocompatible and with potential applications ranging from environmental remediation and catalysis to drug formulation and tissue engineering.^[20] In this paper, we report how combining the PG and LMWG gives a multicomponent system. The two networks can be spatially organised either: (a) as an extended standard vial-filling gel with interpenetrating networks, or (b) as well-defined core-shell structured gel beads (or worms). Surprisingly, given the many uses of alginate and the versatility of LMWGs, reports of hybrid gels combining an alginate PG with LMWGs are rare, and in all cases standard gels were made.^[21] To the best of our knowledge, this is the first time a PG has imposed spherical shape onto an LMWG, thus yielding core-shell supramolecular gel beads (Fig. 2).

The LMWG, DBS-CONHNH₂, was synthesized as previously reported.^[20a] This LMWG forms hydrogels at low concentrations (0.3% wt/vol) using a heat-cool cycle. Low

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Figure 2. Schematic representation of the preparation of DBS-CONHNH₂/alginate multicomponent gels. (1) DBS-CONHNH₂ is suspended in an aqueous solution of sodium alginate. (2) The suspension is heated until complete dissolution of the LMWG. To obtain a hybrid gel with extended interpenetrating networks, the hot solution was left to cool to room temperature, allowing the DBS-CONHNH₂ network to form. An aqueous solution of CaCl₂ (5% - 1 ml) was then added on top of the gel (3a) to diffuse in, crosslink the alginate and form the second gel network (4a). Alternatively, the hot solution was added to an aqueous solution of CaCl₂ dropwise or as a continuous stream to form gel beads or (3b) worms/strings (4b), respectively. Note: The gels were coloured pink using food colouring to be better visualised.

viscosity sodium alginate PG is commercially available and as described above, can be triggered to form gels by CaCl₂. Since the two gels have orthogonal assembly methods, we reasoned a specific spatial arrangement of the two networks within the hybrid LMWG/PG gel could be imposed (Fig. 2).

Initially, to demonstrate the orthogonality of the two gelators, the DBS-CONHNH₂/alginate interpenetrating network hydrogel was obtained using a stepwise approach (Fig. 2 panel 4a) combining an aqueous suspension of DBS-CONHNH₂ (0.3% wt/vol) with sodium alginate (0.5% wt/vol). Heating ensured complete dissolution of the LMWG, with gelation being triggered on cooling. Once the DBS-CONHNH₂ gel had formed, an aqueous solution of CaCl₂ (5% wt/vol – 1 mL) was added to the top of the gel and allowed to diffuse through it, causing cross-linking and gelation of the alginate. The gel properties are briefly summarised below.

Macroscopically, the thermal stability, evaluated via a simple tube inversion method indicated that alginate increased the gel-sol transition temperature (T_{gel}) from 86°C for DBS-CONHNH₂ gel (0.4% wt/vol) to >100°C, i.e., the alginate PG network improves thermal stability. In terms of mechanical properties, oscillatory rheology using parallel plate geometry indicated that the DBS-CONHNH₂ hydrogel (0.4% wt/vol) has an elastic modulus (G') of 800 Pa, the alginate gel (0.4% wt/vol) has a G' of 490 Pa, whereas two-component gels at similar loadings displayed higher G' values (>5000 Pa) - the two networks thus support each other, increasing stiffness (Table S2, Figs. S15-S23). Similar effects are frequently observed for interpenetrated network polymer gels.^[22] Furthermore, hybrid gels obtained using low alginate concentrations were more resistant to strain than gels formed by the individual components, with a linear viscoelastic region (LVR) that extends up to ca. 50% strain in contrast to ca. 6.5% for an equivalent amount of calcium alginate and 25% for the gel formed only by DBS-CONHNH₂. Higher alginate concentrations made the hybrid gels more brittle. The loading of alginate thus allows optimisation between G' (stiffness) and resistance to strain (brittleness). Tunable mechanical properties of this type are of great use in cell culture applications.^[4]

On the nanoscale, scanning electron microscopy (SEM) and transmission electron microscopy (TEM) indicated that DBS-CONHNH₂ and calcium alginate both formed extended nanofibres, ca. 20-40 nm and 40-60 nm in diameter respectively (Figs. S8 and S9). The two-component interpenetrated network gel exhibited long nanofibers with diameters ca. 20-50 nm, consistent with both LMWG and PG networks being present – the networks could not be differentiated because of their relatively similar fibre diameters.

On the molecular-scale, IR spectroscopy (Fig. S2) indicated that the O-H alginate stretch (3390 cm⁻¹), shifted to 3370, 3362 and 3351 cm⁻¹ in the two-component gel obtained using 1.0%, 0.5% and 0.3% wt/vol of alginate, respectively, combined with 0.3% wt/vol of DBS-CONHNH₂. As the relative loading of LMWG increases, the alginate O-H band thus progressively shifts to smaller wavenumber, suggesting non-covalent interactions between DBS-CONHNH₂ and alginate in the hybrid gel, providing evidence for interaction between the networks, in support of rheology. In the presence of alginate, the O-H (3282 cm⁻¹) and N-H (3167 cm⁻¹) stretches of DBS-CONHNH₂ were broadened, also supportive of interactions with the alginate network.

Having determined these two gel networks could indeed be assembled in a stepwise manner, we then targeted LMWG/PG hybrid gels with spatially constrained organisation – specifically core-shell gel beads (Fig. 2, panel 3b, Fig. 3a). We used the same quantities of DBS-CONHNH₂ and sodium alginate, but after heating, the resulting hot solution was added dropwise to aqueous CaCl₂ (5% wt/vol). Small gel beads (Fig. 3b) rapidly formed on calcium-induced cross-linking of the alginate chains, with simultaneous self-assembly of DBS-CONHNH₂ on cooling. The beads were then quickly removed from the mixture. To make the method reproducible and obtain gel beads of similar dimensions, each gel bead was prepared by adding 20 μ L of hot alginate/DBS-CONHNH₂ solution. We combined DBS-CONHNH₂ (0.3% wt/vol) with different alginate concentrations and established that 0.5%





Figure 3. Images of hybrid DBS-CONHNH₂/Alginate gel beads. (a) Schematic diagram of hybrid gel bead; (b) Photograph of hybrid gel beads (droplet size 20 µl), adjacent to a ruler (scale, cm); (c) Optical microscopy of cross-section of hybrid gel bead (droplet size 20 µl), scale bar 500 µm); (d) Optical microscopy of cross-section of hybrid gel bead (droplet size 1 µl, scale bar 150 µm); (e) Optical microscopy of cross-section of hybrid gel bead (droplet size 1 µl, scale bar 150 µm); (e) Optical microscopy of cross-section of hybrid gel bead (droplet size 1 µl, scale bar 150 µm); (e) Optical microscopy of cross-section of hybrid gel bead (scale bar 1 µm); (f) SEM image of hybrid gel bead (scale bar 500 µm); (g) SEM image of hybrid gel bead surface (scale bar 1 µm); (h) SEM image of interior cross section of hybrid gel bead (scale bar 1 µm).

wt/vol was the minimum PG concentration required to isolate spheroidal gel beads. They could also be made with higher alginate concentrations (*i.e.* 0.75% wt/vol and 1.0% wt/vol), but at lower concentrations ($\leq 0.3\%$ wt/vol) they were more irregular.

The gel beads had diameters of 3.0-3.6 mm (Fig. 3b). The theoretical diameter (d) of a sphere of a known volume (V) is obtained using: $d = 2 * \sqrt[3]{3V/4\pi}$. Since for each gel bead a volume of 0.020 mL (= 0.02 cm³) was used, spheres of 0.336 cm (3.36 mm) diameter were predicted – the observed bead diameters therefore agree with expectations. The diameter was varied by simply changing the volume of liquid added dropwise to CaCl₂. Using 5 and 1 µL volumes, we obtained gel beads with diameters of 1.6-2.0 mm and 0.75-1.0 mm respectively (Fig. 3d). Simple optical microscopy clearly indicated core-shell structures (Figs. 3c and 3d). Further optical microscopy on the gel beads cut in half, embedded in resin and dyed with toluidine blue indicated a clear difference between the interior volume and the outer shell in the hybrid gel bead cross section (Fig. S7).

Scanning electron microscopy (SEM, Fig. 3f) provided insight into the nanoscale morphologies of the bead surface (Fig. 3g) and cross-section (Fig. 3h). Samples were prepared by freeze-drying to minimise drying effects. DBS-CONHNH₂/alginate and alginate gel bead surfaces appeared 'wrinkled' (Figs. 3g, S12 and S13) and densely packed consistent with a highly crosslinked calcium alginate shell. The SEM image of the cross-section of the hybrid gel beads shows an extended nanofibrillar network in the core of the bead (Fig. 3h), consistent with incorporation of the LMWG in self-assembled form inside the bead.

By varying the mode of addition of the hot solution containing the LMWG/PG mixture to CaCl₂, the gels could be formed into other shapes, e.g. worms (Fig. 2, panel 4b). Worms were prepared by adding the hot alginate/DBS-CONHNH₂ solution to the CaCl₂ solution as a thin stream rather than dropwise. Stupp and co-workers also used calcium chloride solution to induce the formation of gel worms,^[23] although in their case, a peptide amphiphile was used as the self-assembling unit, that was, itself stiffened as a result of interactions with calcium ions – no PG was present to mediate the process. Our data are consistent with a model in which, as the hot solution is added dropwise into calcium chloride, the periphery is rapidly converted into a calcium alginate crosslinked shell. As the system cools, the LMWG then assembles within this sphere (or worm) to form a self-assembled gel interior. In this way, the calcium alginate PG effectively acts as a 'vessel' or mould that contains the self-assembling LMWG. This prevents the LMWG from uncontrolled assembly into an extended vial-filling gel, and hence yields discrete shaped and structured LMWG/PG objects.

To quantify the amount of DBS-CONHNH₂ incorporated into each gel bead, a simple ¹H NMR experiment was used. Ten beads were isolated and dried under vacuum. The resulting solid was dissolved in DMSO-d₆, dissolving all the DBS-CONHNH₂ but not alginate, so the LMWG can be determined by ¹H NMR. Acetonitrile (CH₃CN) was used as an internal standard, and the concentration of LMWG was hence calculated by comparing the integrals of relevant resonances (DBS-CONHNH₂ aromatic protons: δ = 7.53 and 7.83 ppm, and the acetonitrile CH₃ group: δ = 2.09 ppm) (Fig. S1). In principle, 50 gel beads (20 μ l volume each) could be prepared from 1 mL of water containing DBS-CONHNH₂ (0.3% wt/vol, 6.32 µmoles) and sodium alginate (0.5% wt/vol). If the DBS-CONHNH₂ was fully incorporated and evenly distributed into the gel beads, each bead should contain ca. 0.12 µmoles of LMWG. The NMR study showed that the amount of LMWG in each gel bead was ca. 0.11 µmoles. This experiment was highly reproducible, and we therefore reason that >90% of the LMWG is incorporated within the LMWG/PG gel beads demonstrating the efficiency of this fabrication method.

IR spectroscopy (Figs. S2 and S3) indicated that in the hybrid gel beads, the O-H and N-H stretches of DBS-CONHNH₂ were broadened, and the alginate O-H stretch shifts from 3390 cm⁻¹ to 3352 and 3341 cm⁻¹ (with 1.0% and 0.5% wt/vol of alginate, respectively). These shifts are similar to those described for the interpenetrated gels described above.

To demonstrate one possible use of these spatiallyconstrained hybrid gels, we explored catalysis. Gels have great potential in catalysis as a result of their solvated nature, and the ability of small molecule reagents to diffuse through them – indeed gels can be considered intermediate between homogeneous and

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heterogeneous catalytic systems, combining the advantages of both.^[24] We recently reported that DBS-CONHNH₂ hydrogels achieve efficient *in situ* reduction of precious metals to yield gels with embedded metal nanoparticles (NPs).^[20c] Furthermore gels with embedded palladium nanoparticles (PdNPs) can catalyse Suzuki-Miyaura cross-coupling reactions.^[25] We were interested to see if the presence of alginate influenced Pd uptake or catalysis and demonstrate advantages of the gel bead formulation.



Figure 4. (a) UV-Vis spectra of Pd uptake by Pd-hybrid gel beads (3.00 mg DBS-CONHNH₂ in 0.5 mL H₂O, 0.5 mL 1% alginate, 1 mL 5% CaCl₂); (b) Amount of Pd embedded within the gel beads; (c) TEM image of hybrid gel beads with PdNPs, scale bar 200 nm; (d) SEM image of hybrid gel beads with PdNPs, scale bar 0.5 μ m.

Gel samples were left to interact with aqueous PdCl₂ (3 mL, approx. 5 mM), and at specified times, the supernatant PdCl₂ was analysed by UV-Vis (Figs. 4a and S25-27) to determine the remaining concentration of Pd(II) and thus, the amount of Pd incorporated within the gel. The calcium alginate gel itself could also incorporate Pd(II), in agreement with literature reports.^[26] However, based on the colour of the Pd-loaded calcium alginate gel being yellow, the incorporated Pd is clearly still in the +2 oxidation state (Fig. S30). On the other hand, when DBS-CONHNH₂ was present in the hybrid gel, the gel changed to dark brown/black suggesting not only Pd(II) incorporation, but in situ reduction to Pd(0) (Fig. S30). When the gel was prepared as hybrid gel beads, Pd uptake was faster compared with the extended interpenetrating network gel in vials, presumably due to the greater relative surface area of the beads - a black colour, consistent with reduction of Pd(II) to Pd(0) NPs was again The total amount of Pd within the DBSobserved CONHNH₂/alginate gels was ca. 33% of that in our previously prepared DBS-CONHNH₂/agarose gels.^[25] This agrees with the proposal above that there are interactions between DBS-CONHNH₂ and alginate networks - we suggest these somewhat limit the ability of the acylhydrazide to reduce Pd(II) to Pd(0). The formation of PdNPs was confirmed by TEM and SEM (Figs. 4c, 4d S28 and S29), with the NPs being attached to the gel fibres (where the acyl hydrazide groups are located) and mostly spherical with diameters <5 nm.

The catalytic activity of DBS-CONHNH₂/alginate gels loaded with PdNPs was studied in a standard Suzuki-Miyaura cross-

coupling reaction between 4-iodotoluene and phenylboronic acid (0.8 mmol scale).^[25] When we used the whole amount of extended interpenetrating network DBS-CONHNH₂/alginate gel (3 mg of DBS-CONHNH₂ and 1 mL of 1% alginate) containing ca. 12 µmol of Pd (1.2 mol%), and performed the reaction in the vial in which the gel was formed, we obtained the desired product 2a in 98% yield after stirring at 50°C for 24 h - however, we note that under these stirred conditions, the gel was broken down. The reaction was then performed without stirring, using just one single hybrid gel bead as catalyst (ca. 0.4 µmol of Pd, 0.05 mol%). Pleasingly, product 2a was obtained in 99% yield after 24 h. This clearly demonstrates that these hybrid gel beads have high catalytic potential, and that even a single bead can effectively catalyse the Suzuki-Miyaura reaction (molar ratio of catalyst:reagent = 1:2000). The conversions obtained using these DBS/CONHNH₂/alginate hybrid LMWG/PG gel beads (99% after 24 h using 0.05 mol% Pd) were very similar to those obtained and reported previously using simple DBS-CONHNH₂/agarose hybrid gels (93% after 18 h with 0.05 mol% Pd), suggesting encapsulation within the gel bead is not having an adverse effect on catalytic performance. To demonstrate some scope of these catalytic gel beads, we also performed reactions with a range of other substrates to give 2b-2f in good yield (Scheme 1).



Scheme 1. Suzuki cross-coupling reaction using a single Pd-hybrid gel bead. Reaction conditions: 4-lodoarene (0.80 mmol), phenylboronic acid (0.96 mmol), K₂CO₃ (1.60 mmol), EtOH (3 mL), H₂O (1 mL) and Pd-Hybrid Gel Bead (prepared using 1 mL of 1% alginate; containing ~ 0.05 mol% of Pd). The reaction was carried out without stirring at 50°C for 24 h. Compound **2a** was made using a single gel bead recycled 5 times. Conversions by ¹H NMR.

Although the PdNP gels showed excellent catalytic activity, they could not be easily removed from the reaction. We attempted to increase their mechanical stability by increasing the amount of alginate (1 mL of 2% alginate solution) or using high viscosity alginate (1 mL of 1% alginate solution), but the gel bead could not be removed with a spatula after reaction. We therefore simply left the gel bead in the reaction vial, removed the reaction mixture by Pasteur pipette, washed the gel bead with diethyl ether and water, and charged the reaction vial with fresh starting materials. In this way, it was possible to re-use a single Pd-hybrid gel bead five times (Scheme 1), with high conversion and yield,

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pleasingly demonstrating the recyclabillity and reuse of these gel beads.

We tested the Pd-leaching from these beads (ESI Section S11) and found some palladium was leached into the solvent during reaction. At the end of reaction, if the solution was removed from the bead and charged with different Suzuki reaction substrates, then the second Suzuki reaction would proceed to >90%, even in the absence of the bead. Leaching is greater than from our previously reported agarose hybrid hydrogels (34% Suzuki coupling achieved using the filtrate).^[25] We suggest this results from Pd in the alginate shell being less effectively-bound, and the greater relative surface area of the small beads used here. Nonetheless, a significant amount of Pd is clearly retained within the beads, because, as described above, they can be reused in the reaction 5 times (an overall molar ratio of catalyst:reagent = 1:10000), and the gel beads can definitely be considered as the source of Pd required for reaction.

Overall, it is evident the LMWG retains its fundamental Pd remediation and catalysis properties within these shaped and structured core-shell beads. As such, this fabrication method is a very simple way of imposing shape onto an active and functional self-assembled gelator. The core-shell hybrid gel beads are a straightforward and efficient dosing form for these catalytic gels – one single bead can be placed into the reaction vessel to facilitate the Suzuki-Miyaura cross coupling and the product easily extracted. This would therefore be an effective way of supplying catalytic gels in a simple physical form, which is easy for the enduser to employ in synthesis. This clearly demonstrates the advantage of combining a functional LMWG with a PG that plays the role of imposing defined shape and structure onto the overall system.

In conclusion, we report spatial control over LMWG assembly by combining a LMWG (DBS-CONHNH₂) and a PG (alginate) to form spherical core-shell gel bead structures (or worms). Combining alginate with DBS-CONHNH₂ enhances thermal stability and rheological performance. The mechanical properties of the hybrid gel can be tuned by alginate concentration, giving gels with a range of stiffnesses, and optimisable strain resistance, suggesting potential applications in (e.g.) cell culture. The LMWG (DBS-CONHNH₂) retains its unique properties within the hybrid gel, such as the ability to reduce Pd(II) to Pd(0) NPs in situ, thus creating catalytic gel beads. Gel beads could be simply added into a Suzuki-Miyaura reaction, with just a single bead being able to facilitate reaction. The ease of dosing these shaped and structured gel beads demonstrates an advantage of this approach - fusing the function of an active LMWG with the shaping potential of a PG. We suggest that this hybrid gel approach using calcium alginate to form gel beads should be broadly applicable to a wide range of different LMWGs in order to formulate them into gel spheres, and work in this direction is currently underway in our laboratories. This is therefore a very simple, highly versatile platform technology that could see widespread use in extending the range of LMWG applications. In addition to working to extend the range of gelators incorporated within these beads, we are also investigating further control to yield micro/nano-sized gel beads, and demonstrating the full potential scope of encapsulated shaped and structured LMWG materials, thus opening up even more wide-ranging new applications.

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RESEARCH ARTICLE

Supramolecular gel beads – alginate can be used to enforce spherical core shell structures onto catalytic gels self-assembled from low-molecularweight gelators



Carmen C. Piras, Petr Slavik and David K. Smith*

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Self-Assembling Supramolecular Hybrid Hydrogel Beads