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Hard and Soft Capsules: From Branched Polymers to Controlled Release via Gels

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Summary: Supramolecular gels, made from the combination of telechelic poly (ethyleneglycols) (PEG's) and trivalent poly(isobutylenes) with terminal matching hydrogen bonds were prepared and their rheological properties were investigated. Addition of poly(N-isopropylacrylamide) as thermosensitive polymer was included into the gel-capsules in amounts of 10 w%, producing gels with strongly thermally-responsive properties. Additionally, dansyl-dyes with two different endgroups (either an hydrophobic endgroup or a multiple hydrogen bond) were encapsulated into the gels as mimicks for pharmaceutically active substances. Monitoring their diffusion by UV-dependent measurements allowed to tune the diffusion and thus the release properties of the gel. The generated supramolecular gels will allow the selective encapsulation and triggered release of various pharmaceuticals and biologically active targets.

Keywords: gels; self assembly; supramolecular structures; triggered release

Introduction

Supramolecular gels are built from self associating structures (polymers, oligomers, organic molecules), bound together via supramolecular interactions (mostly via hydrogen bonds and hydrophobic interactions).[1,2] In recent investigations we have been describing concepts for the encapsulation of biologically active substances into capsules, together with their targeting via magnetic forces.[3] Our approach relies on strong noncovalent hydrogen bonding systems, which can act in a A-B type fashion to assemble different types of materials into (microphase) separated polymeric networks (see Figure 1). We are following this concept by generating exact telechelic three-arm star polymeric building blocks, where directed hydrogen bonds (Hamilton-receptor/barbituric acid, comprising a binding strength of $\sim 10^5$ M^{-1}) are attached to each of the (trivalent) chain ends, with the trivalent polyisobutylenes (PIB) acting as crosslinking systems, together with bivalent telechelic poly(ethyleneglycols) (PEG) as hydrophilic counterparts. Gel materials with phase microphase separated structures, able to incorporates supraparamagnetic nanoparticles can be generated. In the present publication, poly(N-isopropylacrylamide) (PNIPAM) is mixed into the supramolecular gel in order to impart additional thermoresponsive properties, provided by the coil to globule transition of PNIPAM. Moreover, the inclusion of small organic compounds is investigated by monitoring diffusional processes, enabling to tune the release of small molecules from the gel-material.

Rheology

In order to monitor the mechanical behavior of the formed gels, dynamic rheology experiments were performed. Gels were

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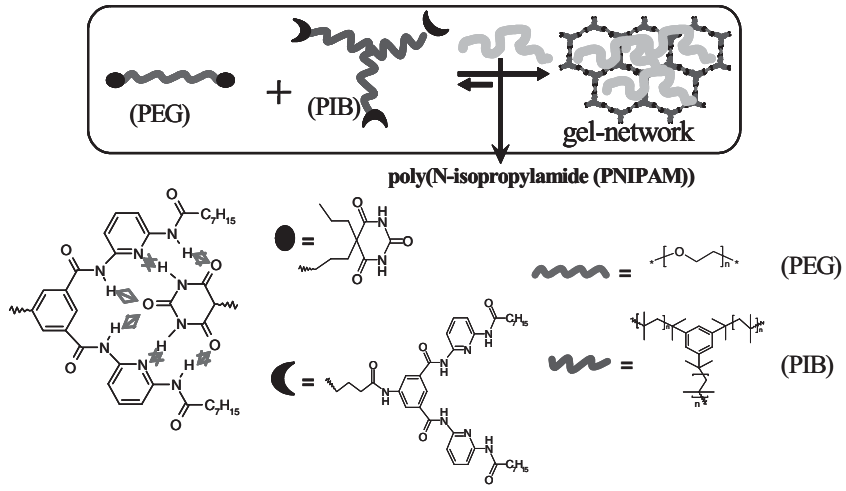

Figure 1.
Concept for the formation of supramolecular gels, made from trivalent hydrophobic (PIB) and bivalent hydrophilic (PEG) telechelic polymers via selective hydrogen bonding interactions. PNIPAM is incorporated in amounts of 5–20 wt% during gel formation.

prepared by mixing stoichiometric amounts of the components (telechelic PIB and PEG – for preparation see citations[2] and[3,4] via combination of living polymerization methods and azide/alkine-"click"-reactions;[5] M_n (PIB) = 5210 g mol^{-1}, $M_w/M_n = 1.09$; M_n (PEG) = 2000 g mol^{-1}, $M_w/M_n = 1.06$); mixture = 1/1 with respect to their hydrogen bonding endgroups) as a 10 wt% solution in chloroform, whereupon gelation occurred spontaneously. Poly (N-isopropylacrylamide) ($M_n = 46\,500$ g mol^{-1}; $M_w/M_n = 1.5$; prepared by free radical polymerization; added amount: 5 wt%) was added to the gelating mixture as solution, achieving a homogeneous distribution within the gel. Subsequently, the rheological properties were monitored using a modular compact rheometer (Physica MCR 100), applying a shear rate of ($d(\gamma)/dt = 10$ s^{-1}), a stress amplitude of 2.5 mrad at ~1 Hz, following G′ and G″ (see Figure 2a). It can be clearly seen that both G′ and G″ reach a plateau-value of 2.5×10^3 Pa and 4.3×10^3 Pa respectively, indicative of reaching an equilibrium state after about 100–120 minutes. The gelation process therefore is relatively slow, indicative of a slow chain ordering process, induced by the formation of the hydrogen bonding system and the corresponding network formation. In comparison to the gel without PNIPAM, the values of G′ and G″ are comparable hinting at an only minor disturbance of the gel-structure by the incorporated amount of PNIPAM (5 wt%).

Since Poly (N-isopropylacrylamide) (PNIPAM) exhibits a remarkable volume change in response to temperature changes, temperature-dependent rheological experiments after heating to 45 °C were performed. Measurements were performed at 20 °C, 35 °C, corresponding with the lower critical solution temperature of PNIPAM, then heating to 45 °C and again cooling to 20 °C (Figure 2b). At higher temperatures the gel-formation is perturbed ($G'' > G'$) (at 35 °C and 45 °C ($G'' > G'$)) with an increase in the dynamic moduli values: at 35 °C, values of $G' = 3.32 \times 10^3$ Pa and $G'' = 5.1 \times 10^3$ Pa are reached, observing values of $G' = 4.8 \times 10^3$ Pa and $G'' = 6.7 \times 10^3$ Pa at 45 °C. Finally, the gel sample was cooled down to 20 °C (see Figure 2b), leading initially to a higher value of the storage modulus ($G' = 9.7 \times 10^4$ Pa), with values decreasing over time, reaching a cross-over at approx. 30 min ($G'' > G'$). Clearly, there is an additional thermosensitive feature of the supramolecular gel

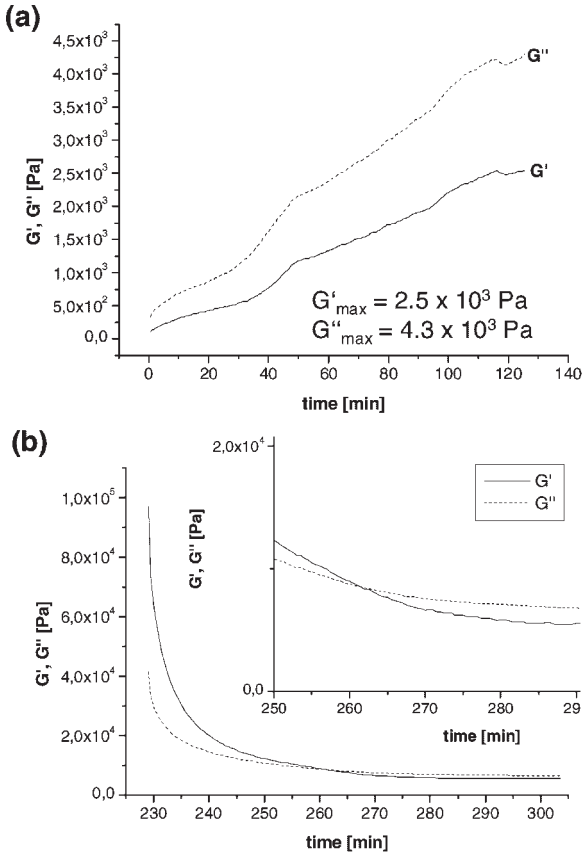

Figure 2.
Dynamic rheology experiments of the supramolecular gel with 5 wt% of PNIPAM. (a) rheological behavior directly after mixing. (b) rheological behavior after heating to 45 °C and cooling to 20 °C. Only the rheological behavior at 20 °C is shown, demonstrating the crossing-over of G′ and G″ during cooling.

induced by the presence of the PNIPAM-polymer.

Diffusion Studies

In order to evaluate the encapsulation properties of the supramolecular gels, fluorescent compounds (dye 1 and dye 2, respectively – see Figure 3) were incorporated into the gel, additionally to the PNIPAM polymer. Both dyes consist of a fluorescent reported moiety (dansyl-residue), with dye 1 comprising hydrophobic properties via the attached n-hexyl chain and dye 2 with a matching hydrogen bonding interaction, able to interact selectively with the supramolecular gel-structure.

Diffusion of the dyes was monitored without PNIPAM (see Figure 4) via UV-spectroscopy (at $\lambda = 298$ nm) at various temperatures, indicating the strong selectivity of the interacting **dye 2** with the gel matrix, leading to a more than a factor 10 slower diffusion of **dye 2** out of the gel (in comparison to **dye 1**). Thus a strong influence of the attached functional group on the diffusion process can be observed, in accordance with the underlying supramolecular interaction.

The influence of PNIPAM on the diffusion process was studied in similar experiments. Figure 5 shows the results for the diffusion of dye 1 in the gel with the incorporated of PNIPAM. As shown in Figure 5 (graph (a)) the incorporation of

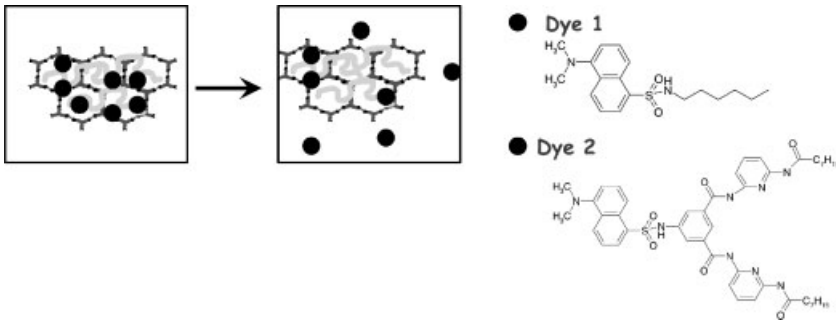

Figure 3.
Concept for studying the diffusion of encapsulated dansyl-dyes out of the supramolecular gel, with PNIPAM as thermoresponsive element.

5 wt% of PNIPAM leads to a faster diffusion of the dye, as compared to the pure supramolecular gel without the PNIPAM polymer. Graph (b) shows the same experiment with 20 wt% of PNIPAM, indicating a similar behavior as in the case of 5 wt% of PNIPAM. At higher temperatures (graph (c) in Figure 5) the diffusion process

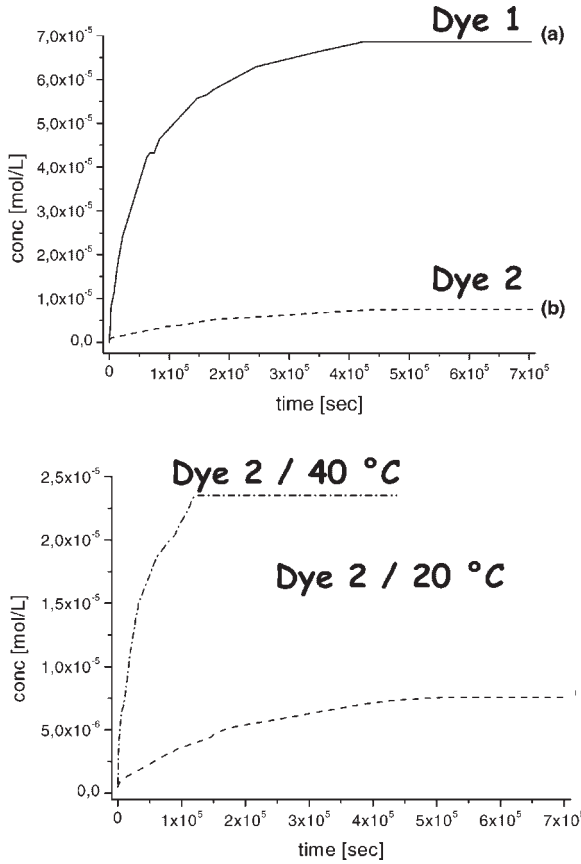

Figure 4.
Diffusion of dye 1 and dye 2 out of the supramolecular gel. (*top*): diffusion of dye 1 and dye 2. (*bottom*): diffusion of dye 2 at 20 and 40 °C, respectively.

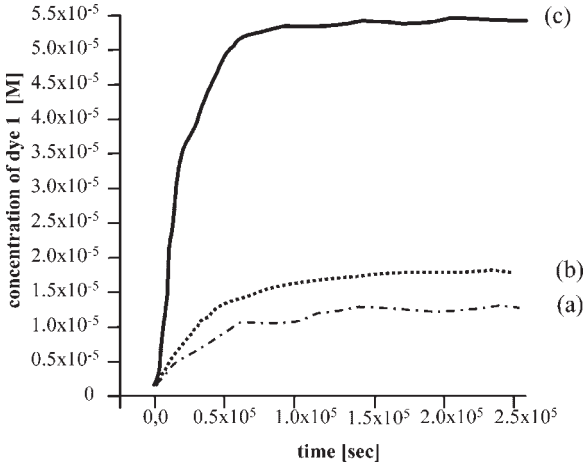

Figure 5.
Diffusion of dye 1 out of supramolecular gels with PNIPAM. (a) supramolecular gel with 5 wt% PNIPAM and dye 1 at 20 °C. (b) supramolecular gel with 20 wt% PNIPAM and dye 1 at 20 °C. (c) supramolecular gel with 5 wt% PNIPAM and dye 1 at 40 °C.

is strongly enhanced, indicative of the thermoresponsiveness of the PNIPAM polymer and the underlying reversibility of the hydrogen bonds, breaking at higher temperatures.

Conclusion

We have demonstrated capsules built from a supramolecular polymer with incorporated PNIPAM as an additional thermoresponsive element. Inclusion of appropriately functionalized samples can be demonstrated, allowing the tuning of the diffusion of small organic substances out of the gel matrix. This approach opens a new concept for the delivery of pharmaceutically active substances by small changes in temperatures, allowing their temperature-selective delivery.

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