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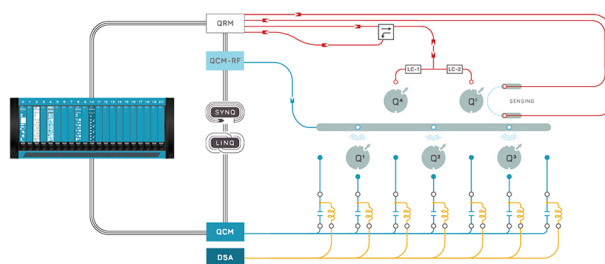
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Loading and release of internally self-assembled emulsions embedded in a magnetic hydrogel

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We have investigated drug loading and release from thermosensitive gel emulsions with external triggering by an alternating magnetic field (AMF) for on-demand drug delivery. Superparamagnetic iron oxide nanoparticles dispersed in gel emulsions were used to study the loading and release capabilities, with the stable nitroxide radical 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) serving as the model drug. AMF activation gave similar results to temperature activation in a water bath at 37 °C, showing that the principal effect of the AMF is a temperature increase without burst release. These results suggest that the system could play an important role in the development of advanced drug delivery. © 2014 AIP Publishing LLC. [<http://dx.doi.org/10.1063/1.4862811>]

Confinement and controlled release of drugs through constrained geometries continue to be an active topic in nanotechnology with a special focus on biopharmaceutical applications.^{1,2} One attractive challenge is to design devices for long-term therapies, with a zero premature release rate, i.e., “on-demand” release patterns. During the ON mode, delivery could be activated with a controlled release rate while during the OFF mode, delivery through continuous leakage should be negligible since too rapid release or “burst release” might lead to more side effects and thus needs to be controlled. Among the potential candidates, a combination of drug carrying nanoporous lipid particles, having intrinsically high surface areas, with stimulus-responsive hydrogels appears particularly promising.

Recently, the development of oil-in-water ISAsomes, a class of channel-forming liquid crystalline media of submicron size, has aroused considerable interest in biotechnological applications.^{3–6} The internal structure of ISAsomes can be tailored by varying the temperature and the concentration of selected additives such as oil.^{7,8} This produces a reversible exchange of water between the inside and outside of the internally confined nanostructures as the temperature is cycled between heating and cooling. It has been recently shown that ISAsomes can be incorporated into a thermo-reversible polymer-hydrogel network.^{4,9} Despite the possible interactions between the polymer chains and the internal structure, the remarkably maintained internal organization enhances their applications. These rather simple but elegant media facilitate the storage of drug-loaded functional particles by controlling

the macroscopic dynamics of ISAsomes and the subsequent drug release by thermomagnetic activation.

Ferrogels are magnetically and thermally responsive hydrogels^{2,10–13} that are swollen by magnetic nanoparticles (NPs). At room temperature and for sizes less than 10 nm, NPs exhibit superparamagnetic properties and under an alternating magnetic field (AMF), they generate heat,^{14–16} which can be used as an external stimulus promoting the structural change of a thermosensitive material with a simultaneous release of entrapped molecules.¹⁷ This mechanism is called thermo-magnetically activated or AMF-triggered release.

In this work, we fabricate and disperse oleic acid-coated and citrated superparamagnetic iron oxide nanoparticles (SPION), in ISAsomes loaded with 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) and a thermally responsive hydrogel, κ -carrageenan (Fig. 1). For the system thus obtained, we then compared the effect of AMF-triggered heating with that of an external temperature increase in a water bath. Electron spin resonance (ESR) spectroscopy was used to monitor the diffusion of TEMPO and to verify whether the molecular dynamics of TEMPO is affected by the composite hydrogel structure.

We first investigated the structure and shape of the hydrophilic citrated and hydrophobic oleic acid-coated SPION. The X-ray diffraction (XRD) confirmed that the crystalline structure is the fcc inverse spinel. Transmission electron microscopy (TEM) analysis revealed a median diameter for the hydrophilic and hydrophobic SPION of 9.0 ± 0.3 nm and 6.0 ± 0.2 nm, respectively.

Zero field cooling/field cooling (ZFC/FC) curves recorded with Superconducting Quantum Interference Device (SQUID) magnetometry at 100 Oe for $5 < T < 300$ K show a behavior characteristic of SPION with a blocking temperature (T_B) higher for hydrophilic SPION than for

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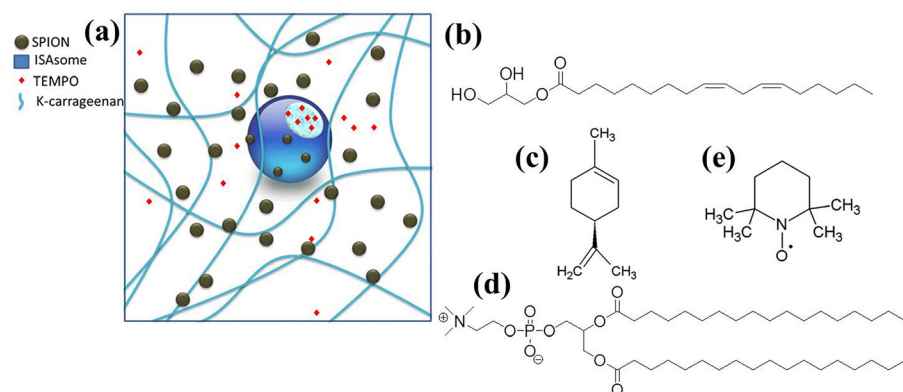


FIG. 1. (a) A schematic representation of the system, and molecules used in ISAsome formulation: (b) monolinolein and (c) R-(+)-limonene, for the initial internal structure, (d) lecithin, providing the stability of the dispersions, and (e) the model drug, TEMPO.

hydrophobic ones. Taking a mean T_B at the maximum of the ZFC curve, the ratio of T_B for hydrophilic and hydrophobic SPION is 3.4 roughly corresponding to that of the median particle volumes. A broadening of the ZFC curve is observed for the hydrophilic SPION, probably due to larger polydispersity. However, since the hydrophilic SPION are not separated by an oleic acid shell,¹⁸ in contrast to the hydrophobic ones, the interparticle interactions may also be responsible for the larger T_B , the broadening of ZFC curve, and the flattening of the FC curve.¹⁹

The internal structure of the ISAsomes at different stages of preparation as well as after adding TEMPO and hydrophobic SPION measured by small-angle x-ray scattering (SAXS) confirmed that the micellar cubic internal structure of the droplets is maintained although a small shift in the lattice parameter was observed from 16.7 to 16.9 nm. This could reflect the incorporation of oleic acid in the ISAsomes. The mean hydrodynamic diameter of these dispersions, measured by dynamic light scattering, is constant within experimental error: 195 ± 21 nm for ISAsomes without additional molecules, 175 ± 16 nm for ISAsomes with TEMPO, and 197 ± 14 nm for ISAsomes with TEMPO and SPION.

Finally, the emulsions were trapped within a thermo-reversible hydrogel made of κ -carrageenan to provide a hydrophilic material with κ -carrageenan undergoing a reversible gel/sol transition when T is increased above the upper critical solution temperature. In terms of swelling, the mixed gel absorbs 75% less water than κ -carrageenan alone, and a degradation of rheological properties is reported. The polymer chains are not covalently cross-linked and after a certain time of immersion in water the physical gel degrades when the swelling is at its maximum.

The diffusion of TEMPO in the composite hydrogel was measured by ESR. The unpaired electron spin in a nitroxide radical delocalized over the NO group interacts with the nuclear spin of ^{14}N ($I = 1$). This gives rise to a characteristic ESR spectrum of TEMPO that consists of a triplet of resonant features whose spectral parameters largely depend on the solvent (Fig. 2(a)). In particular, the ESR lines of TEMPO are broader in nonpolar media, the peak-to-peak line widths being of 2.8 G in oil and 1.6 G in water. The hyperfine splitting changes from 17.2 G in water to 15.4 G in oil, in agreement with previous work²⁰ and allows us to distinguish TEMPO localized in the dispersed phase of ISAsomes + hydrophobic SPION from that in the aqueous phase of ISAsomes, SPION, and hydrogel. The presence of

TEMPO in both phases is confirmed by a splitting of the high-field hyperfine line (Fig. 2(b)), similar to that observed in phospholipid membranes,²¹ implying that at a permeation barrier exists between water and oil at the lecithin-water interface. In the absence of such barrier, the two lines would be mixed by rapid motion and not resolved. The diffusion barrier is expected to be related to the nature of the surfactant used to stabilize the emulsion. Moreover, the presence of SPION broadens further the ESR signal of TEMPO by dipole-dipole interactions (Figs. 2(c) and 2(d)). The overall wide-swept ESR spectrum of this system is shown in Fig. 2(c) and the narrow spectral region corresponding to the ESR signal of TEMPO is shown in the inset to Fig. 2(c).

The partition ratio $K_d = \frac{c_{oil}}{c_{water}}$, with c_{oil} and c_{water} the TEMPO mass concentrations in oil and water, can be calculated from H and P in Fig. 2(b). In the case of the emulsion, we obtain $K_d = 40$, thus confirming that TEMPO has a greater affinity for the hydrophobic phase.^{22,23}

The detection of undistorted sharp ESR lines shows that TEMPO is not trapped at interfaces but remains fully mobile in both water and oil and therefore the out-of-gel diffusion is controlled by the gel morphology, as well as by the slow

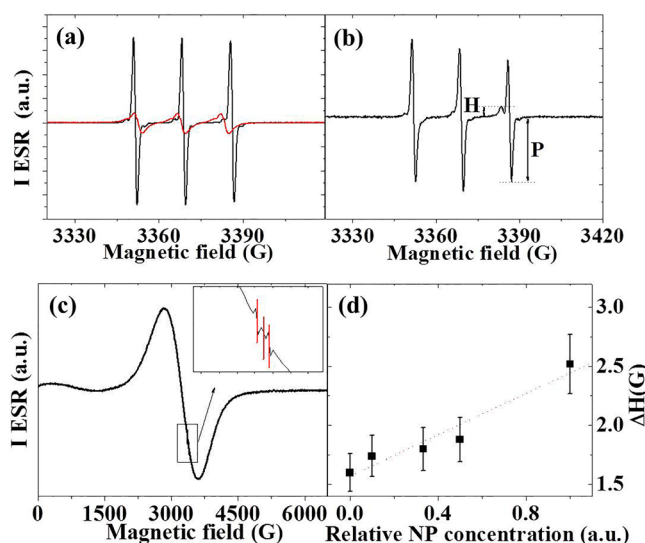


FIG. 2. ESR signals of: (a) TEMPO in non-polar oil (red trace) and polar water (black trace) environments; (b) TEMPO in ISAsomes: H and P denote the heights of the ESR peaks corresponding to the TEMPO fraction in oil and in water, respectively; (c) The ESR spectrum showing the overlapped signals of TEMPO and SPION; (d) The ESR line width of the high-field hyperfine feature of TEMPO vs the relative concentration of SPION in water ($[\text{TEMPO}] = 0.6 \text{ mmol.L}^{-1}$, $[\text{SPION}]_{\text{max}} = 2.5 \text{ g.L}^{-1}$).

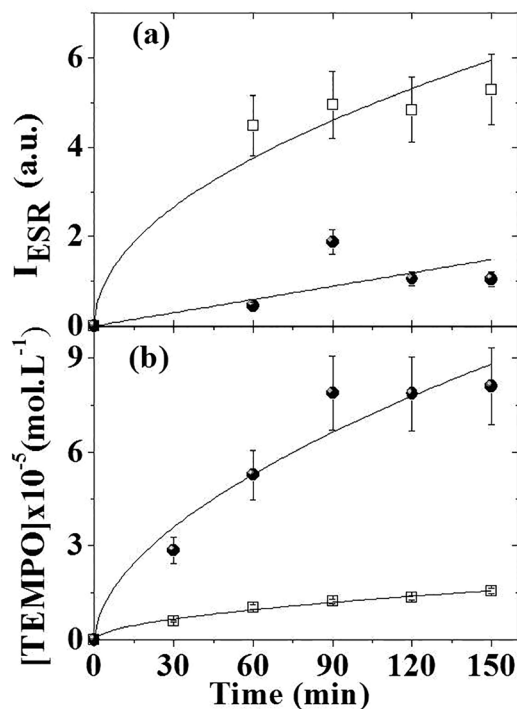


FIG. 3. (a) SPION and (b) TEMPO release from hydrogel matrix, as monitored by ESR, with (□) or without (●) ISAsomes at room temperature as a function of time. Full lines correspond to $n=0.5$ for SPION release from ISAsome containing gel, $n=1$ for SPION release from hydrogels without ISAsome, $n=0.54$ for TEMPO release with ISAsome, and $n=0.56$ for TEMPO without ISAsome.

passage through the lecithin barrier. The short-time diffusion rate of TEMPO is 1.04×10^{-6} and $5.42 \times 10^{-6} \text{ mol.L}^{-1}.\text{s}^{-1}$ for magnetic hydrogels with and without ISAsomes, respectively (Fig. 3(b)).

If we consider the simplest case of the theory of drug release from hydrogel matrices,^{24,25} e.g., the Fickian diffusion without external barrier of a solute completely dissolved in the matrix, we can calculate $M(t)$, the total amount of drug released at time t as

$$M(t) = 2A\sqrt{Dt/\pi}, \quad (1)$$

where A is the initial solute concentration per unit volume ($A < c_s$, the solute solubility in the matrix) and D the solute diffusion coefficient.²⁶ When $A > c_s$, Higuchi's analysis²⁷ of solid particle dissolution gives

$$M(t) = \sqrt{2Dc_s \left(A - \frac{c_s}{2} \right) t}. \quad (2)$$

However, the real cases deviate very often from the above theoretical predictions of the time dependence of $M(t)$. Therefore, commonly, a phenomenological model is used,²⁵ which describes the drug release with a semi-empirical equation

$$M(t)/M_0 = Ct^n, \quad (3)$$

where M_0 is the absolute cumulative amount of drug released at $t = \infty$, C is a constant incorporating structural features of the system, and n is the release exponent, indicative of the

mechanism of drug release. It turns out that $n=0.5$ for diffusion-controlled release in planar geometry, $n=1$ for swelling or dissolution, and $0.5 < n < 1$ for the intermediate case where both mechanisms are present. In our case, the best fit gives $n=0.54$ for TEMPO diffusion from the gel with ISAsomes, thus showing that the drug release is mainly due to pure diffusion and implying that the release mechanism is the same in both cases. Note that ISAsomes were not detected by ESR in the top water layer, which suggests that swelling and dissolution at the interface remain moderate on our time scale.

Both reductions of the diffusion coefficient D and of the initial drug concentration can play a role in limiting TEMPO release. We first consider the role of ISAsomes as drug reservoir following Higuchi's description.²⁷ Assuming that the pseudo-steady-state approximation is valid (which supposes that dissolution rate is fast), Eq. (1) applies. For $A = 2 \times 10^{-4} \text{ mol.L}^{-1}$, and $c_s = A/K_d$ ($K_d = 40$), we have

$$M(t) \approx \sqrt{\frac{2\pi}{K_d}} A \sqrt{\frac{Dt}{\pi}}. \quad (4)$$

Equation (4) is quite different from Eq. (1), which applies for the hydrogel without ISAsomes. The reduction factor of $2/\sqrt{2\pi/K_d} \approx 5$ due to the presence of ISAsomes is remarkably close to our experimental result of 5.2, suggesting that the main parameter governing release from ISAsomes-loaded hydrogel is K_d and that D is not significantly changed.

The observed large decrease in water swelling capacity of the ISAsomes-filled hydrogel implies that the physical cross-link density increases due to interaction with the ISAsomes. If so, the porosity and the solute diffusion would decrease,²⁸ which is not consistent with the increased diffusion of the SPION out of the ISAsomes-containing gel and the degradation of the mechanical properties. The latter, in fact, suggests that the porosity increases with the content of ISAsomes, probably due to chain-clustering effects similar to those reported by Walther *et al.*²⁸ Such a pore opening would explain the diffusion-controlled release of SPION, described by a $t^{1/2}$ dependence of $M(t)$, whereas SPION release out of the gels without ISAsomes takes place through the swelling-dissolution at the water interface ($n=1$). Despite the increase in porosity, the change in diffusion coefficient is not significant, and we conclude that TEMPO diffusion is regulated by ISAsomes via the partition ratio.²⁰ Introducing ISAsomes decreases the initial loading of TEMPO in the water phase of the hydrogels. Thus, ISAsomes play a double role of both drug reservoir and drug concentration limiters.

For the thermally activated diffusion, the tube containing the gel was submitted to an AMF with an amplitude of 88 mT, and a frequency of 108 kHz. A fluoroptic temperature probe was inserted in the gel making it possible to record the temperature variations with time. Two successive AMF triggered activations were performed (Fig. 4(b)): the first lasted 20 min from 10 to 31 °C and the second 40 min from 4 to 34 °C. We followed the initial heating slope from RT (or after cooling to 4 °C), until the magnetic heating reached the desired temperature, and then slowed down the diffusion by

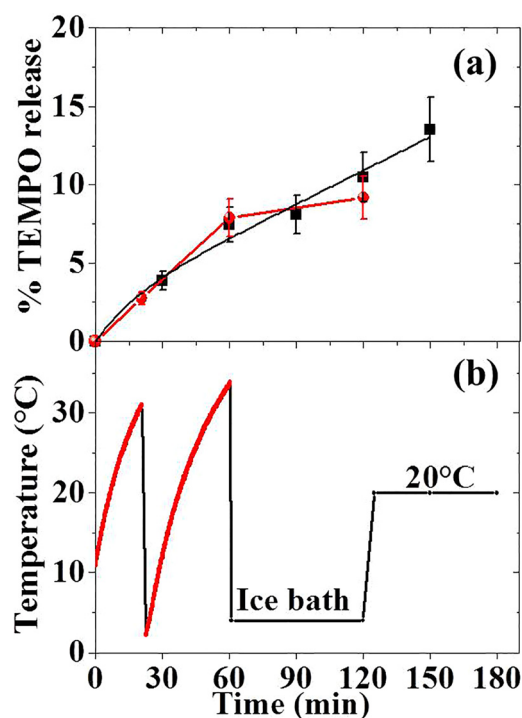


FIG. 4. (a) The percentage of TEMPO release after active AMF triggering as a function of time with two consecutive AMF activations followed by cooling in an ice bath (red circles), compared with passive activation in a water bath at 37 °C (black squares); (b) temperature profile of the AMF-triggered steps.

cooling the gel in an ice bath. The local heating by SPION leads to the diffusion of TEMPO out of the gel in the water phase (Fig. 4(a)). We calibrated the thermal activation of TEMPO diffusion with measurements in a temperature-controlled water bath, shown for comparison in Fig. 4(a). The AMF-triggered diffusion and temperature-triggered diffusion at 37 °C gave similar results, showing that the main effect of the AMF is a temperature effect without burst release. The concentration of the released model drug, TEMPO, was independent of the mechanism of heating. Baeza *et al.*² inferred the presence of hot spots generated by the local heating of SPION under AMF and studied the release process from porous nanoparticles at the stabilized temperature of 32 °C, during a prolonged magnetic heating for several hours. Since we are examining diffusion from a macrogel with fewer interfaces than the porous nanoparticles, the presence of hot spots is expected. The emulsion acts as a storage reservoir with the hot spots destabilizing the lecithin barrier interface with the outer gel and TEMPO diffusing out of the hydrogel. A tunable “on-demand” burst release could be obtained by varying the field exposure duration and amplitude, the SPION magnetic properties, and higher SPION loadings.

We also compared the effect of temperature on TEMPO release by fitting data with Eq. (3) at 20 °C and 30 °C for hydrogels with and without ISAsomes: in the first case, C increased by 30%, and only by 12% without ISAsomes. We attribute this difference to the increase of the partition ratio with temperature.²¹

We conclude that ISAsomes immobilized in nanocomposite hydrogels play the role of both drug reservoir and drug delivery limiters allowing a controlled sustained release of drugs, represented here by TEMPO. The ESR results show

that lecithin plays a key role in controlling TEMPO diffusion. This behaviour is expected to be independent of the molecular details of the lipophilic drug, at least for small molecules whose mobility is not hampered by interfacial trapping.

No confinement or interfacial trapping effects were observed with TEMPO in ISAsomes, despite the impact on the internal structure; TEMPO remains mobile in the oil/lipid phase, with exchange rates comparable with those in the bulk. The out-of-gel diffusion is governed by the partition ratio K_d . Loading with SPION allows an AMF-triggered drug delivery. The combination of a temperature-responsive reservoir system with ISAsomes having a high surface-to-volume ratio and a magnetically responsive hydrogel provides a promising device for drug delivery, with sustained release provided by AMF triggering. The temperature increase created by the AMF suggests that this device could play an important role in the development of advanced drug delivery systems for cancer treatment.

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