SUPPLEMENTARY MATERIAL A: Physicochemical Membrane Characterization

The chemistry, structure, and magnetization properties of the composite nanogelferrofluid membranes were analyzed using x-ray photoelectron spectroscopy (XPS), xray diffraction (XRD), transmission electron microscopy (TEM), and magnetization measurements.

X-Ray Photoelectron Spectroscopy (Fig. 1a in article): X-ray photoelectron spectroscopy (XPS) was performed using an Axis Ultra DLD (Kratos Tech.). Samples were mounted on a rod in the pretreatment chamber of the spectrometer which was evacuated at room temperature. Spectra were excited by a monochromatized AlK α source (1486.6 eV) run at 15 kV and 10 mA. A pass energy of 20 eV was used for individual peak regions. Survey spectra were measured using an 160 eV pass energy. Analysis of peaks was performed with software provided by the manufacturer, using a weighted sum of Lorentzian and Gaussian components after background subtraction. Binding energies were referenced to the internal C 1s (284.9 eV) standard. Deep profile experiments were accomplished by sputtering the sample surface using an Ar⁺ ion beam operating at an incident energy of 5 keV and current of 20 mA. The sputter rate was estimated to be 1 nm/min based on measurements using Ta₂O₅/Ta films under identical sputter conditions.

Elemental concentration profiles of the membranes (the raw data from the XPS analysis) are shown in Supplementary Figure 1.





The relative concentrations of ethylcellulose, nanogel, and ferrofluid in the membrane as a function of etching depth were calculated based on these elemental data and are shown in Figure 1a. The ferrofluid concentration was calculated based on the measured elemental concentration of iron while the nanogel concentration was estimated according to the atomic concentration of nitrogen (since nitrogen is only found in the nanogel).

X-Ray Diffraction (Fig. 1b in article): The crystallite size and lattice spacing of magnetite in the ferrofluid particles entrapped inside the membranes was analyzed via x-ray diffraction using a Rygaku/Max System diffractometer using CuKα radiation

 $(\lambda = 1.5418 \text{ Å})$ and a graphite monochromator Crystallite sizes were calculated from the diffraction spectra based on the Scherrer equation (Equation 1)

$$D = \frac{0.9\lambda}{\Gamma_{hkl} \cos(\theta_{hkl})} \tag{1}$$

where *D* is the crystallite length, λ is the x-ray wavelength, and Γ_{hkl} is the full width at half maximum (FWHM) of the diffraction peak at the angle θ_{hkl} .

Figure 1b indicates that the XRD spectrum of the membrane closely matches that of magnetite, confirming that the ferrofluid particles have a single phase magnetite crystal structure. To calculate the reported crystallite size, a least squares fitting procedure was used to fit Equation 1 to the large amplitude peak at $2\theta \sim 35$ in the experimental XRD spectrum. The result of this fitting procedure is shown in Supplementary Figure 2; the adjusted R² value of 0.982 suggests a good fit to the experimental data.



Supplementary Figure 2. XRD data fitting: Scherrer equation fit to the maximum amplitude peak in the XRD spectrum of the composite membrane

Based on this analysis, the average crystallite size of ferrofluid in the membrane was estimated as 11.8 nm. This particle size within the nanometre size range facilitates significant magnetic heating via hysteresis losses in an oscillating magnetic field.

Transmission Electron Microscopy (Fig. 1c in article): Transmission electron microscopy measurements were performed by embedding a portion of the membrane in an EpofixTM cold-setting resin. The slices were cut at 30-60 nm thickness using a RMC MT-XL ultramicrotome with a diamond blade (Drunkker Ultra-microtome knife, ElementsixTM advanced diamond). The sliced sections were mounted on carbon copper grids and subsequently imaged at 200 kV in a JEOL-2000 FXII microscope. Elemental analysis of image features was performed using a computerized energy dispersive (EDS) x-ray analysis system (INCA 200 X-Sight, Oxford Instruments).

Representative transmission electron micrographs of the membrane and the EDS spectrum of the ferrofluid at the location indicated in the TEM image are shown in Figure 1c in the article and Supplementary Figure 3 below.





The TEM image indicated that the average diameter of the ferrofluid particles in the membrane was less than 20 nm, with most particles in the range of 10-20nm. This corresponded well with the XRD result of 12 nm and the magnetization result of d < 20nm. While the ferrofluid was effectively distributed throughout the membrane, several clusters of ferrofluids were found. This clustering may be a result of capillary forces drawing the ferrofluid particles together upon drying or clustering of the hydrophilic, PEO-coated ferrofluid inside or around the more hydrophilic nanogel phase within the

membrane. The latter hypothesis cannot be confirmed since the nanogel could not be identified in the TEM image due to the lack of contrast between the nanogel and ethylcellulose phases. While aggregation of the ferrofluid in the ethanol suspension cannot definitively be ruled out, aggregation is considered unlikely since individual ferrofluid particles are clearly visible in the TEM image. Maintaining individual ferrofluid particles in the membrane phase would improve the effectiveness and uniformity of magnetic induction heating within the membrane. The membrane also contained trace amounts of carbonaceous materials, titanium, and silicon which may be derived from dust which settled in the membrane over the long evaporation time or impurities present in the reagents or the ferrofluid or nanogel components of the membrane. The copper detected in the sample was an artefact of the copper grid used to collect the TEM image.

Magnetization Measurements (Fig. 1d in article): Magnetic measurements as a function of temperature and field were performed in a commercial SQUID MPMS magnetometer (Quantum Design). Zero-field-cooled (ZFC) and field-cooled (FC) curves were measured between 5 K and 280 K using a cooling field of H_{FC} = 100 Oe. Data were obtained by first cooling the sample from room temperature in zero applied field (ZFC process) to the base temperature (5 K). A magnetic field was then applied and the magnetization was measured with increasing temperature up to T = 280 K. After the last point was measured, the sample was cooled again to the base temperature maintaining the same magnetic field (FC process). Magnetization versus temperature data were then

measured over increasing temperatures. Hysteresis loops were measured at 5 K and 280 K for applied fields -5 T < H < 5 T.

Magnetization curves for membranes containing 25% nanogel, 28% ferrofluid, and 47% ethylcellulose are shown in Supplementary Figure 4.

Supplementary Figure 4. Magnetization of composite membranes: Magnetization (M) curves for composite membranes measured at 5 K and 280 K. Inset: magnification of the low-field region to show the coercivity (H) at both temperatures.

The isothermal curves measured at low and high temperature are consistent with the presence of single-domain particles in a blocked state. At T = 5 K the coercive field $H_C =$

346±4 Oe is consistent with values found for Fe₃O₄ nanoparticles of similar size¹. At room temperature, the coercivity decreased almost to zero (H_C = 13±5 Oe), suggesting the sample is close to its blocking temperature. The saturation magnetization values M_S are 28 emu/g and 31.3 emu/g at 280 and 5 K respectively. Correcting these values for the measured mass concentration of dried ferrofluid nanoparticles entrapped in the membrane, the saturation magnetization values are 96.5 and 107.9 emu/g dry ferrofluid particles at 280 K and 5 K respectively. These values are similar to those measured for bulk magnetite (M_S = 93-96 emu/g at 280 K)^{2,3}. Furthermore, the iron particles embedded in the membrane have the expected single-domain magnetic properties of superparamagnetic nanoparticles.

The single-domain structure of the magnetic nanoparticles used in this work is further supported by the magnetization data measured in ZFC and FC modes, shown in Supplementary Figure 5. The observed increase in magnetization values as the temperature increases after being cooled in zero-field is expected for the progressive unblocking of the single-domain particles due to the increasing thermal energy. The data collected in field-cooling mode (FC) remains essentially constant along the whole temperature range, indicating no further alignment of the particles after cooling in a 100 Oe applied field. The change of slope in the ZFC curve as the temperature approaches room temperature and the small H_C values observed at 280 K suggest that the ferrofluid particles have their unblocking temperature (T_B) near room temperature⁴. This unblocking temperature suggests the magnetic particles have a size on the order of ~20 nm, in agreement with both the TEM imaging and XRD results.

Supplementary Figure 5. Magnetization versus temperature for composite membranes: Magnetization (M) data acquired in ZFC and FC mode for composite membrane as a function of temperature (T); H = 100 Oe

Based on these observations, the magnetic nanoparticles heat via the mechanism of power absorption and subsequent magnetic relaxation of single-domain nanoparticles due to the coupling between the magnetic moment of the nanoparticles μ and the applied AC magnetic field H^5 .

SUPPLEMENTARY MATERIAL B: Mechanical Characterization of Membranes

Tensile and compressive mechanical tests were performed on magnetic nanogel composite membranes using an Instron 4411 tensile tester operating at a strain rate of 10 mm/min. For either test, rectangular strips of composite membrane with a gauge length of 18 mm and a cross-sectional dimension of 5 mm were cut and clamped to the Instron tester. Membranes were tested both dry and wetted after 24 hours of rehydration. Four replicates are performed for each test under each condition (dry and wetted) tested.

Tensile testing was used to measure the critical strain of the membrane and the peak force tolerated by the membrane prior to fracture. Representative tensile test results for dry and wetted composite membranes are shown in Supplementary Figure 6.

Supplementary Figure 6. Tensile force versus % strain data for dry and wetted composite membranes

Dry membranes were more brittle than wetted membranes and tolerated strains of $3.4\pm0.4\%$ at a peak fracture force of 18 ± 3 N. Wetted membranes were significantly more plastic, tolerating strains of $12.6\pm2.7\%$ prior to fracture and supporting peak forces of 11 ± 1 N and peak tensile stresses of 11 ± 1 MPa prior to fracture. These values are comparable to those of a native human tendon⁶ and are far in excess of what would be encountered in a typical implant into connective tissue (particularly for the wetted membrane which is more representative of the membrane state *in vivo*). Thus, the membrane appears to be mechanically stable against fracture.

Compressive testing was used to measure the forces associated with bending the membranes to assay the membrane stability against applied flexural strains. Representative results, expressed in terms of the overall force required to compress the membrane strip as a function of the percentage compression of the strip, are shown in Supplementary Figure 7. The membranes were extremely flexible and pliable in both their dry and wetted states, with near-zero compressive forces required to compress the membranes for all but extremely high % compression values at which the membrane folded down upon itself and behaved as a spring to resist further compression. Dry membranes buckled at % compressions in the range of 60-70% (the minimum observed in the dry membrane compression data in Supplementary Figure 7) but did not fracture under compression. In contrast, wet membranes continued to fold continuously until overall compressions of >90%, at which point further compression was physically blocked by the folded membrane compressed between the Instron clamps. This result suggests that flexural strains exerted on the membranes (in particular, the wetted membranes which would be present in vivo) will not mechanically disrupt the membrane.

The high tensile and compressive strains tolerated by the membranes strongly suggest that composite membranes may be appropriate for the fabrication of drug depot-based devices which can safely contain large quantities of drug over a long period of time.

SUPPLEMENTARY MATERIAL C: Nanogel Phase Transition Behavior

The thermal phase transition temperature behaviour of the nanogel synthesized for use in physiologically-responsive composite membranes is shown in Supplementary Figure 8.

Supplementary Figure 8. Nanogel phase transition behaviour: Particle size versus temperature profile for nanogels used in membrane fabrication

The microgel underwent a ~400 size change from the "off" state (microgel swollen, 37 °C) to the "on" state (microgel collapsed, 50 °C), with a volume phase transition temperature of ~40 °C. It should be noted that ~60% of the total volume phase transition is complete at 41 °C while >90% of the volume phase transition is completed by 43 °C. Thus, relatively small temperature changes above physiological temperature induced large changes in the microgel particle size.

SUPPLEMENTARY MATERIAL D: FT-IR Analysis of Membrane Triggering

Attenuated total reflectance FT-IR spectroscopy was applied to confirm that the volume phase transition of the PNIPAM-based nanogels occurs as expected while the nanogels are entrapped within the microgel-ferrofluid composite membranes. Infrared spectra were measured using a Vertex 70 Bruker FTIR spectrometer equipped with a DTGS detector, a horizontal attenuated-total-reflection accessory with thermal control, and a diamond crystal (Golden Gate Heated Single Reflection Diamond ATR, Spectra-Teknokroma). The background absorbance of water was used as a reference which was automatically subtracted from the sample absorbance. The membranes, maintained in the wet state throughout the analysis, were measured at 30 °C, heated to 50 °C, cooled back to 30 °C, and then re-heated to 50 °C. Spectra were measured at each temperature point 10 minutes after the target temperature was reached. Spectra were collected by averaging 40 scans in the 4000-600 cm⁻¹ wavenumber range at a resolution of 4 cm⁻¹. Data analysis was performed using OPUS software (Bruker Optics).

Attenuated total reflectance FTIR spectra of the amide region of the spectrum (1650-1500 cm⁻¹ wavenumbers) of hydrated membranes above (50 °C) and below (30 °C) the volume phase transition temperature of the microgel are shown in Supplementary Figure 9 for two complete thermal cycles. The principal contribution to the Amide I signal (wavenumber 1600-1650 cm⁻¹) is the carbonyl stretching vibration while the Amide II signal (wavenumber 1500-1550 cm⁻¹) is mainly attributable to N-H bending vibrations⁷. The wavenumber of the maximum of the Amide II band shifted from 1536 cm⁻¹ at 30 °C to 1530 cm⁻¹ as the temperature increased (red shift). This result is in agreement with

previous IR studies of PNIPAM-based hydrogels^{8,9}. The observed red shift could be explained by the presence of stronger NH···OH₂ hydrogen bonds at low temperature, a consequence of the significantly higher affinity of the microgel for water in the swollen state relative to the collapsed state⁸. The intensity of the 1546 cm⁻¹ shoulder also decreases relative to the 1536-1530 cm⁻¹ vibration at temperatures exceeding the volume phase transition temperature of the nanogel. This observation could be related to a change in the ratio between the free form of non-hydrogen bonded N-H (1530 cm⁻¹) and the intramolecular hydrogen bonded N-H (1546 cm⁻¹) as the temperature increased⁷.

Supplementary Figure 9. FT-IR analysis of membrane transitions: Infrared spectra for nanogel membranes at 30 °C (below the phase transition temperature, membranes in "off" state) and 50 °C (above the phase transition temperature, membranes in "on" state)

The Amide I band shifted to higher wavenumbers at the higher temperatures (blue shift). This blue shift has been previously reported ^{9,10} and could be attributed to changes in the types of hydrogen bonds formed within the nanogel phase above and below the volume phase transition temperature. At 30 °C, the main component of the Amide I band (~1612 cm⁻¹) could be attributed to C=O···H-O polymer-water hydrogen bonds (i.e. the nanogel is highly swollen and has a high affinity for water); conversely, at 50 °C, the peak at ~1630 cm⁻¹ increased in intensity due to an increase in C=O···H-N polymer-polymer hydrogen bonding (i.e. in the collapsed state, the nanogel has a lower affinity for water and intermolecular hydrogen bonding becomes more probable)⁹. It must be noted that the CH₃ and CH₂ stretching vibrations (2990-2820 cm⁻¹ range) were unaffected by temperature.

These results were consistent over a range of different nanogel contents (21-28% nanogel), ferrofluid contents (19-30% ferrofluid), and membrane thicknesses (0.15-0.3mm thickness). Thus, the nanogel phase transition appears to proceed normally when nanogels are entrapped inside the composite membranes, accounting for the differential flux profiles observed as a function of temperature or magnetic heating.

SUPPLEMENTARY MATERIAL E: Magnetic Flux Apparatus

Power absorption (SPA) data were acquired using a system designed and built to generate oscillating magnetic fields working at f = 220-260 kHz and field amplitudes from 0 to 20 mT. Supplementary Figure 10 shows a schematic diagram of the apparatus used.

The system consisted of three main components: the induction coil, the power supply, and the water closed-circuit. The induction coil was a water-cooled, seven-turn solenoid having a 4 cm internal diameter and 10 cm height, manufactured from 8 mm diameter commercial copper tubing. In the axial space of the solenoid, a semi-adiabatic sample space was defined by inserting a thermally-insulating polyurethane sleeve into the solenoid, leaving an internal cavity (~2 cm³) that enabled the insertion of a 2 mL PTFE reservoir which contained the triggerable membrane-capped device. The membrane-capped device used for magnetic flux experiments is shown in Supplementary Figure 11.

Supplementary Figure 11. Implantable membrane device: Picture of membranecapped capsules used for magnetic flux testing

The reservoir was connected to a warmed water circulator (maintained at 37°C) using 2 mm diameter nylon tubing. Calculations of the magnetic field inside this cavity using finite-element simulation software showed field homogeneity better than 0.5 % from the center to any point of the sample. The water flow was controlled by a peristaltic pump (P1 Amersham Biosciences) which allowed precise flux control from 0.6 to 500 mL/h. Experiments were carried with constant flux of 2.2 mL/min. Temperature data were measured using a fiberoptic temperature probe immune to RF environments and were digitally registered in a PC as a function of time. The temperature probes were located inside the sample holder, approximately 3 mm away from the downstream membrane cap. Samples were collected at pre-determined intervals and analyzed using an Agilent 8453 UV/VIS spectrophotometer operating at 487 nm wavelength.

SUPPLEMENTARY MATERIAL F: Kinetics of Magnetically-Activated Release

To evaluate the potential for predictably varying the dose of drug delivered from the devices based on the duration of the magnetic pulse, multiple magnetically-activated release cycles were performed and the resulting concentration versus time curve (Figure 2b) was integrated numerically to calculate the total mass of drug released per cycle. This value was then divided by the duration of the "on" pulse to determine the mass rate of drug release from the devices during each cycle. Supplementary Table 1 shows the kinetics of drug release from the membrane-based devices over the four thermal cycles tested.

Supplementary Table 1. Total mass of sodium fluorescein release and rate of drug release during each magnetic cycle shown in Figure 2b

Cycle	Duration of "On" Cycle	Total Mass Released	Rate of Drug Release
	11	(mg)	(mg/min)
1	35	0.43	0.012
2	40	0.47	0.012
3	57	0.69	0.012
4	75	0.83	0.011

The mass of drug release correlated well with the duration of the "on" cycle ($R^2 = 0.995$), with the rate of drug release in each cycle varied by less than 10% (0.012 ± 0.001 mg/mL). Together, these observations suggest that the dose of drug delivered via the devices can be reproducibly controlled by changing the duration of the magnetic pulse.

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