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Ellipsoidal Microcavities: Electromagnetic Properties, Fabrication, and Use as Multispectral MRI Agents[†]

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Micro- and nanoscale structuring of electromagnetically susceptible materials underpins many recent advances in biomedical imaging, sensing, and treatment.^[1,2] From plasmonic nanoparticles^[3] and surface plasmon enhanced detectors,^[4] to microengineered multispectral magnetic resonance imaging (MRI) agents,^[5–7] tailored material geometries enable new functionalities through locally modified fields and amplified signals. This communication introduces a new class of such field-shaping microstructure: the ellipsoidal microcavity. Ellipsoidal particles are already of considerable interest in mathematical packing and granular media studies,^[8] and have been shown to self-assemble into anisotropic materials with unique mechanical and optical properties.^[9–11] Here we emphasize that there are additional electromagnetic advantages to their use that stem from their unique ability to generate truly uniform local electromagnetic fields. This communication discusses these ellipsoidal field properties and introduces a new microfabrication protocol that produces almost mathematically exact ellipsoids and ellipsoidal cavities. In addition to providing a new route to colloids with well-defined eccentricities that may enable novel self-assembled structure geometries, when hollowed out, the remaining ellipsoidal cavities' uniform fields makes them ideal candidates for a new class of tunable, multispectral MRI agents.

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Fields within electromagnetically polarized objects depend on applied polarizing and induced depolarizing fields. Because depolarization depends on object geometry, uniform applied fields and homogeneous object compositions do not necessarily yield uniform internal fields. It is only objects bounded by surfaces of second degree, that is, only ellipsoids, that have uniform depolarization fields^[12] and that therefore permit completely uniform internal fields. Since these internal fields are physically inaccessible, however, here we introduce ellipsoidal cavities, which we define as the cavity that results when one ellipsoidal volume is removed from within another (Figure 1).

A goal of this work is to employ such cavities as a new form of MRI agent. Therefore, we focus on magnetizable ellipsoids, but equivalent arguments apply also to electrically polarizable ones. With the cavity comprising one ellipsoid subtracted from another, in the limit of fully saturated ferromagnetic ellipsoids, the generated cavity field becomes equal to the difference between internal fields that would have resulted for the outer and inner ellipsoids individually. Uniform ellipsoid fields therefore imply uniform cavity fields. In particular, when saturated, ellipsoid magnetizations are equal and cancel to leave an ellipsoid cavity field contribution equal simply to the difference in magnetic depolarization, or demagnetization, of outer and inner ellipsoids. Demagnetization factors for prolate and oblate ellipsoids magnetized parallel to their axes of revolution (z-axis in Figure 2a), are:^[13]

$$D_{\text{prolate}} = \frac{1}{k^2 - 1} \left[\frac{k}{\sqrt{k^2 - 1}} \ln \left(k + \sqrt{k^2 - 1} \right) - 1 \right] \quad (1a)$$

$$D_{\text{oblate}} = \frac{k^2}{k^2 - 1} \left[1 - \frac{1}{\sqrt{k^2 - 1}} \arcsin \left(\frac{\sqrt{k^2 - 1}}{k} \right) \right] \quad (1b)$$

where k is the ratio of ellipsoid major to minor axes, related to ellipsoid eccentricity through $e = [1 - k^{-2}]^{1/2}$. Note that the demagnetization is independent of overall size. Therefore, for the field within a magnetically saturated ellipsoidal cavity to differ from the applied field, the cavity's inner and outer ellipsoidal boundaries should have different eccentricities. Additionally, to render the cavity accessible, either the shell material should be porous, or the inner and outer boundaries should overlap at some point, leading to an opening in the shell. This is possible with either coincident or offset ellipsoid centers. Given their uniform demagnetizations even asymmetric ellipsoidal cavities (as suggested in Figure 1) will still generate uniform fields. Moreover, this field uniformity can be substantially preserved even for widely open elliptical shells. This initially counterintuitive result is possible because overlapped ellipsoids of locally similar curvatures (as suggested in Figure 2) can yield large openings with only minimal deviations in shell material thicknesses from the mathematically ideal limiting cases.

Although ellipsoidal microparticles are commonly made by stretching^[14–16] or irradiating^[17] microspheres, to produce open ellipsoidal microcavities with differing inner and outer eccentricities we introduce a new fabrication scheme. The scheme relies on the observation that, for particular incident angles, evaporation onto a rotating sphere can yield an almost mathematically exact ellipsoid. Subsequent removal of the spherical core leaves

an ellipsoidal microcavity with inner and outer boundaries defined by a sphere (zero-eccentricity ellipsoid) and a finite-eccentricity ellipsoid of revolution, respectively.

Evaporation onto spheres is not new. Using such deposition, various two-sided Janus particles^[18] and plasmonically active hemispherical shells^[19,20] have been demonstrated. However, there has been no focus on how shell profiles might be microengineered to generate uniform electromagnetic fields within the shell cavity. Transforming a sphere into an eccentric ellipsoid requires particular deposited material thickness profiles. Figure 2a shows an xz -plane through the middle of a sphere of radius R positioned within an ellipsoid of revolution that has semi-axes $R \cdot (1 + \varepsilon_a)$ and $R \cdot (1 + \varepsilon_b)$ and that has been offset vertically by a distance δ . The cross-sectional circle and ellipse are described by $x^2 + z^2 = R^2$ and $[x/(1 + \varepsilon_a)]^2 + [(z - \delta)/(1 + \varepsilon_b)]^2 = R^2$, respectively, with $\delta = \varepsilon_b R$ if circle and ellipse bases coincide as suggested in the figure. In polar coordinates this translates into a circle parameterized by $r_{circle}(\theta) = R$ and an ellipse by $r_{ellipse}(\theta)$ determined from $[r_{ellipse}(\theta) \sin \theta / (1 + \varepsilon_a)]^2 + [(r_{ellipse}(\theta) \cos \theta - \delta) / (1 + \varepsilon_b)]^2 = R^2$. The thickness, or height, $h(\theta)$, of material normal to the spherical surface required to transform the sphere into the ellipsoid is $r_{ellipse}(\theta) - r_{circle}(\theta)$. For a thin material shell with ε_a and ε_b much less than unity, this yields the required thickness profile

$$h(\theta) = \delta \cdot \cos \theta + \varepsilon_a R \sin^2 \theta + \varepsilon_b R \cos^2 \theta. \quad (2)$$

To first approximation, the thickness of material evaporated onto a surface scales with the projection of the incident fluence on that surface. For spherical surfaces this typically yields cosine-like thickness profiles that poorly match the desired $h(\theta)$ profiles. However, if material is obliquely evaporated onto a sphere while the supporting substrate rotates about its surface normal (see Figure 2b), good approximations to $h(\theta)$ become possible. Consider an arbitrary point, P , on the surface of such a rotating sphere centered at the origin. By rotational symmetry P can be chosen without loss of generality to have azimuthal angle $\varphi = 0$, giving position and surface normal vectors proportional to $\{\sin \theta, 0, \cos \theta\}$. Provided there is direct line of sight to the evaporative source, the instantaneous thickness of material deposited normal to the surface at point P is proportional to the dot product $\{\sin \theta, 0, \cos \theta\} \cdot \{\sin \theta_1 \cos \varphi_1, \sin \theta_1 \sin \varphi_1, \cos \theta_1\}$. Here the latter vector reflects the (negative) incident flux direction in terms of incident angles, θ_1 and φ_1 . In the rotating sphere's reference frame, θ_1 remains constant but the effective incident azimuthal angle, φ_1 , varies. The evaporation thickness profile, $h_{evap}(\theta)$, therefore becomes:

$$h_{evap}(\theta) = \frac{h_0}{2\pi} \cdot \int_{-\varphi_{limit}}^{\varphi_{limit}} (\sin \theta \sin \theta_1 \cos \varphi_1 + \cos \theta \cos \theta_1) d\varphi_1 \quad (3)$$

Here φ_{limit} restricts integration to those azimuthal angles for which P remains visible from the source and the incident fluence is quantified through h_0 , which represents the thickness of material that would be deposited if that fluence were normally incidence on a planar substrate. For a sphere, φ_{limit} is determined by the range of φ_1 for which the above dot product remains positive, that is, the range satisfying $\cos \varphi_1 - \cot \theta \cot \theta_1$. As can readily be

verified, for $\theta = \pi/2 - \theta_i$, or for $\theta = \pi/2 + \theta_i$, the point P is visible for all φ_i , or for no φ_i , respectively; elsewhere, $\varphi_{\text{limit}} = \arccos(-\cot\theta_i \cot\theta)$, giving the piece-wise form:

$$h_{\text{evap}}(\theta) = \begin{cases} h_0 \cos\theta \cos\theta_i & (\theta \leq \frac{\pi}{2} - \theta_i) \\ = \frac{h_0}{\pi} \left[\sqrt{-\cos(\theta + \theta_i) \cos(\theta - \theta_i)} + \cos\theta \cos\theta_i \arccos(-\cot\theta \cot\theta_i) \right] & (\frac{\pi}{2} - \theta_i < \theta < \frac{\pi}{2} + \theta_i) \\ = 0 & (\theta \geq \frac{\pi}{2} + \theta_i) \end{cases} \quad (4)$$

The evaporation angle, θ_i , and ellipsoid parameters, ε_a and ε_b , can be connected: for coincident sphere and ellipsoid bases, Equation 2 gives $\varepsilon_a = h(\pi/2)/R$ and $\varepsilon_b = h(0)/2R$, yielding, through Equation 4, $\varepsilon_a = (h_0/\pi R) \cdot \sin\theta_i$, $\varepsilon_b = (h_0/2R) \cdot \cos\theta_i$, or, more generally, $\varepsilon_a/\varepsilon_b = (2/\pi) \cdot \tan\theta_i$. Profiles for various θ_i are shown in Figure 2c. For normally incident evaporation Equation 4 reduces, as it must, to $h_{\text{evap}}(\theta) = h_0 \cos\theta$. For $\theta_i \approx 30^\circ$ and $\theta_i \approx 70^\circ - 75^\circ$, however, the resulting evaporation profiles closely follow the required profiles of Equation 2 for generating prolate or oblate ellipsoids with $\varepsilon_a/\varepsilon_b$ equal to $(2/\pi)\tan 30^\circ$ and $(2/\pi)\tan 70^\circ$, respectively.^[21]

The theoretically required and the evaporated profiles overlap so closely that residual mismatches are better gauged by calculating the fields that such evaporatively deposited structures would produce when magnetically saturated. Since ellipsoids generate uniform fields, field inhomogeneities resulting from the evaporatively deposited structures indicate ellipsoidal inaccuracies. Such a field-based metric also suits structure optimization because it includes the deleterious effects on field uniformity of the finite-sized cavity opening. Moreover, because it is experimentally challenging to directly measure nanometer-thin shell thickness variations accurately, comparison between these field calculations and actual experimental NMR spectra provide a means to confirm that real evaporated shell profiles are as predicted. Figure 3 presents the results of such calculations, including histograms of the field intensities in the vicinity of the cavity. Uniform internal fields produce sharp, offset peaks atop a broad background arising from the non-uniform external fields surrounding the cavity. The narrower the peak, the better the internal field uniformity and the more truly ellipsoidal is the structure. While $\theta_i \approx 30^\circ$ provides a good match, for sequential evaporation at $\theta_i \approx 30^\circ$ and at $\theta_i \approx 0^\circ$ the match can become even better and agreement could likely be improved further by combining evaporations at several angles.

While uniform fields result for ellipsoids of any eccentricity, spherical cavities not only support both prolate and oblate shells, but their spherical geometries are also more naturally scalable and easier to fabricate, either lithographically or by routine chemical syntheses that obviate the need for photolithographic patterning. For this first demonstration a lithographic approach was chosen because it conveniently provides monodisperse particles in well-spaced arrays that facilitate oblique evaporations and subsequent NMR characterization. The fabrication begins by optically patterning arrays of circles in a double resist layer. With a photosensitive upper layer but an isotropically developing lower one, resist development yields arrays of undercut cylindrical posts as shown in Figure 4a. Rapid heating above the glass transition temperature of the upper resist, but below that of the underlying resist, leads to upper photoresist reflow^[22]. The undercut profile prevents reflow across the substrate; instead surface tension reshapes the molten cylinders into suspended, energy-minimizing

spherical geometries (Figure 4b). A magnetizable material is then evaporated as described above (Figure 4c). Next, a crosslinkable gel is poured over the sample and covered by a second, transparent substrate (Figure 4d). Exposure through this substrate UV-crosslinks the gel, encapsulating, and therefore lifting off, the metal-coated spheres when the substrates are subsequently separated (Figure 4e). Finally, an oxygen plasma etches away the spherical cores and surrounding gel, leaving the desired microcavities (Figure 4f). Scanning electron micrographs (SEM) alongside in Figure 4 capture various microfabrication stages and show resulting prolate and oblate ellipsoidal microcavities.

As an example of the utility of ellipsoidal microcavities, we show how their uniform fields enable multispectral MRI contrast. Microengineered multispectral MRI contrast agents are a recent development^[5–7] that adds multicolor labeling to the traditionally greyscale medical imaging technology. They are based on magnetic micro- and nanostructures shaped such that their associated field profiles impart discrete shifts to the NMR frequency of the water in their vicinity. Different geometries yield different frequency shifts, resulting in a set of imaging agents distinguishable from one another through their different effective radio-frequency MRI colors. In this way, such multispectral agents enhance MRI through new multiplexed imaging capabilities analogous to those provided by multicolor imaging labels such as quantum dots or plasmonic nanoparticles that have proven invaluable in optical bioimaging fields.

Since NMR precession frequencies are proportional to the magnetic field magnitude, discrete frequency shifting of the local water resonance requires a local field that is of different magnitude to the surrounding field and that is uniform over an extended, water-accessible volume. With their uniform internal fields, magnetizable ellipsoidal microcavities therefore become ideal candidates for such multispectral agents. Given the proportionality between field and frequency, the microcavities' suitability is already evident in the field histograms of Figure 3, which approximate the NMR spectra that would result from water within and around such cavities.

To approximate analytically the NMR shift within the cavity, we Taylor expand Equation 1 obtaining, to first order, $D_{\text{prolate}} = 1/3 - 4(k-1)/15$ and $D_{\text{oblate}} = 1/3 + 4(k-1)/15$. For spheres, $k = 1$, while for prolate and oblate ellipsoids with ε_a and ε_b much less than unity, k is approximately $1 + \varepsilon_b - \varepsilon_a$ and $1 + \varepsilon_a - \varepsilon_b$, respectively. Since the cavity field depends on the difference in ellipsoid demagnetization factors, for magnetization parallel to the ellipsoid axes of revolution both prolate and oblate shells generate cavity fields of magnitude $4J_s \cdot (\varepsilon_b - \varepsilon_a)/15$. Here the constant of proportionality relating demagnetization field to demagnetization factor is J_s , the magnetic saturation polarization density of the material comprising the shell. For proton gyromagnetic ratio, $\gamma = 2\pi \times 42.6 \text{ MHz T}^{-1}$, this gives water NMR frequency shifts, ω , of:

$$\Delta\omega = \frac{4}{15} \cdot \gamma \cdot J_s \cdot (\varepsilon_b - \varepsilon_a) \quad (5a)$$

Alternatively, substituting for $\varepsilon_a = (h_0/\pi R) \cdot \sin\theta_1$ and $\varepsilon_b = (h_0/2R) \cdot \cos\theta_1$, gives the shift in terms of evaporation angles and thicknesses:

$$\Delta\omega = \frac{4}{15} \cdot \gamma \cdot J_s \cdot \frac{h_0}{R} \cdot \left(\frac{\cos\theta_i}{2} - \frac{\sin\theta_i}{\pi} \right) \quad (5b)$$

Frequency shifts can therefore be engineered over broad spectral ranges by switching materials, ellipsoid eccentricities, or shell thicknesses. As examples, three different sets of $R \approx 1 \mu\text{m}$ microcavities were fabricated. Two sets were based on prolate ellipsoids made by sequentially evaporating nickel ($J_s \approx 0.6 \text{ T}$) at $\theta_i \approx 30^\circ$ and at $\theta_i \approx 0^\circ$ (in an approximately 4:1 ratio), up to shell thicknesses corresponding to $h_0 \approx 135 \text{ nm}$ and $h_0 \approx 200 \text{ nm}$; the third set comprised oblate ellipsoids evaporated at $\theta_i \approx 70^\circ$ with $h_0 \approx 450 \text{ nm}$. (These thicknesses are well over an order of magnitude less than the skin-depth of magnetically saturated nickel at NMR frequencies, eliminating any possible RF shielding inside the cavity). Figure 5 displays resulting NMR z-spectra,^[23] which show the frequency-dependent water magnetization saturated out, M_s , as a fraction of initial magnetization, M_0 (see Experimental Section). The observable frequency-shifted peaks verify that the cavities generate substantially uniform interior fields. Additionally, substituting the above parameters into Equation 5b yields positive field shifts corresponding to approximately 300 kHz and 450 kHz for the prolate ellipsoids, and a negative field shift corresponding to approximately -400 kHz for the oblate ellipsoids, all agreeing with observed NMR spectra. Note that while these field shifts equal just a fraction of the applied field (see Experimental Section), in MRI terms they are large, thousands of times greater than NMR chemical shifts, which typically measure a few parts per million. Indeed, together with other microengineered multispectral MRI contrasts agents^[5–7], these ellipsoidal cavities, even with thin shell thicknesses, offer the largest frequency shifts of any ^1H MRI agents. Such large shifts can potentially enable a large number of different ellipsoidal cavity agents, each with different resonant frequency shifts or effective radio-frequency colors, to be spectrally isolated, and therefore simultaneously distinguished, from one another for highly multiplexed MRI.

Despite the above agreement between predicted and observed frequency shifts, present cavity spectral linewidths fall short of their theoretical potential, likely for several reasons. With signals acquired from arrays of microcavities, linewidths broaden if there are any cross-wafer microfabrication variations in cavity shapes. Finite source-to-substrate distances mean that actual evaporation angles and fluences vary across the wafer. Additionally, the assumption of constant θ_i is strictly true only at the wafer center; elsewhere θ_i varies cyclically as the wafer rotates. Fortunately, such variations diminish as distance between evaporation source and substrate is increased. A separate issue is structural (and possibly magnetic) integrity near the cavity openings where wall thicknesses taper to zero. Wall integrity could likely be boosted in future by coating the shell with supporting, non-magnetic material before removing the core. Evaporation angles might also be optimized to compensate for possible thickness cutoff effects near the shell openings.

For signals integrated over multiple agents, distinct frequency shifting assumes all agents aligned and magnetized parallel to one another. Ellipsoids are well-known to naturally align to applied fields,^[9–11] and similar magnetic shape anisotropy can drive the self-alignment of ellipsoidal shells to the MRI field. Whether this alignment is parallel or perpendicular to the

field, however, depends on shell thickness. For concreteness, this communication has considered magnetization along the ellipsoid axis of revolution but for orthogonal magnetization NMR shifts are simply negative one half of those given above, a consequence of demagnetization factors along any three orthogonal axes of any ellipsoid summing to unity.^[13] For an example of orthogonally magnetized microcavities see Supplementary Figure S1.

In conclusion, this communication has introduced a new method to transform spheres into well-defined eccentric ellipsoids and ellipsoidal microcavities. Such non-spherical colloids offer natural potential for novel self-assembled materials. Additionally, with their uniform fields, the ellipsoidal microcavities represent optimal geometries for multispectral MRI agents. If residual structural and microfabrication imperfections can be overcome, they promise a new class of multispectral MRI agent that has excellent spectral resolution and that may be both more readily scalable and more easily produced than any prior alternatives. Finally, we note that ellipsoidal microcavities are not overly dissimilar to plasmonic hemispherical shells^[19] suggesting the possibility of a unique doubly-resonant multi-modal imaging agent offering two simultaneously, yet independently, tunable colors: one in the optical, the other in the MRI radio-frequency spectral range.

Experimental Section

NMR characterization

All spectra were acquired on an 11.7T MRI, except for that of the orthogonally oriented sample (Figure S1b), which was acquired on a 14T MRI more amenable to sample rotation. All spectra are magnetization transfer z-spectra^[23,24] acquired similarly to ones previously described that exploit diffusion-driven signal amplification^[6]. Data for each spectral point were averaged from two integrated on-resonance free-induction-decay acquisitions that each followed 6 s duration preparatory off-resonance irradiation pulse trains comprising 100- μ s long $\pi/2$ pulses separated by 250- μ s delays.

Materials^[25]

Double-layer resist comprised a base layer of LOR-3A (MicroChem) and a top layer of Megaposit SPR-660 (Rohm & Haas), reflowed by rapidly heating to 175° C. Encapsulating gel comprised poly (ethylene glycol) dimethacrylate (MW 200, Polysciences) mixed with 5 % w/w 2,2-dimethoxy-2-phenylacetophenone (Sigma Aldrich), a photoinitiator for UV-crosslinking. All test samples comprised glass substrates supporting 14 x 14 mm² square arrays of nickel ellipsoidal microcavities submerged under 100- μ m deep water. Within each array microcavities were spaced 6.4 μ m apart, reducing magnetic cross-talk and permitting oblique evaporations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1.

Schematic of magnetically saturated ellipsoidal cavity as the difference between two solid ellipsoids. Dotted lines are calculated magnetic B-field lines and show cavity field uniformity. For clarity, the applied magnetizing field (uniform, and directed vertically) is omitted. For the particular case shown, the field generated by the structure opposes the applied field leading to a total cavity field smaller than the applied field. In general, however, the total cavity field can be made less than, equal to, or greater than the applied field by changing the relative eccentricities of the defining ellipsoids.

Figure 2.

Transforming a sphere into an ellipsoid by rotated evaporation. a) Schematic geometry showing thickness profile, $h(\theta)$, of evaporated material that converts sphere to ellipsoid; b) Schematic of rotating evaporation setup; c) Thickness profiles of material deposited onto spheres for various incident evaporation angles θ_i . Theoretically required thickness profiles for creating ellipsoids (dashed curves) closely match those produced by rotated evaporation when $\theta_i = 30^\circ$ and when $\theta_i = 70^\circ$.

Figure 3.

Calculated histograms of magnetic field magnitudes (relative to applied field), simulating NMR spectra in the vicinity of magnetized hollow shells produced by evaporation at various angles onto sacrificial rotating spheres. Broad central peaks arise from inhomogeneous fields around the shells; for special angles around 25–30° and 70–75° evaporation yields approximately ellipsoidal shells that generate uniform internal fields and corresponding shifted peaks (c & f). g) Evaporation at 30° followed by at 0° (in ~ 4:1 ratio) yields a sharp peak indicating an almost perfectly ellipsoidal shell. Insets provide alternate visualization of field uniformity, showing spatial variation in field magnitudes normalized relative to each cavity's central field (with surrounding evaporated shell structure in white).

Figure 4. Microfabricated ellipsoidal microcavities. Left side: schematic of microfabrication protocol (see text). Right side: scanning electron micrographs (SEM) showing arrays of (top to bottom) undercut cylindrical photoresist posts, photoresist spheres formed by surface tension assisted reflow, and resulting prolate and oblate ellipsoidal microcavity structures. Scale bars are 2 μm .

Figure 5.

NMR z-spectra showing experimental ellipsoidal cavity offset resonances. Magnetization transfer z-spectra show fraction of water magnetization saturated out as a function of frequency offset from original NMR water-line for: a) thin prolate ellipsoidal shell; (b) thicker prolate ellipsoidal shell; (c) oblate ellipsoidal shell.