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Self-Assembled Polymer Membrane Capsules Inflated by Osmotic Pressure

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Abstract: We fabricate and characterize capsules that are composite membranes, made of a polymer network stabilized by adsorption to colloids and inflated by osmotic pressure from internal free polyelectrolyte; here, poly-L-lysine forms the network and inflates the capsules. To assess these capsules' properties and structure, we deform capsules using microcantilevers and use finite element modeling to describe these deformations. Additional experimental tests confirm the model's validity. These capsules' resilient response to mechanical forces indicates that loading and shear should be good triggers for the release of contents via deformation. The osmotic pressure inflating these capsules has the potential to trigger release of contents via deflation in response to changes in the capsules' environment; we demonstrate addition of salt as a trigger for deflating capsules. Because these capsules have a variety of release triggers available and the technique used to fabricate them is very flexible and allows high encapsulation efficiency, these capsules have very high potential for application in many areas.

Introduction

Techniques for encapsulation and delivery of active agents are increasingly vital to technologies as varied as drug delivery, functional foods, biomedicine, and "smart" materials.[1−9] Hollow structures, like vesicles or capsules, have high potential for holding sensitive contents until release into the external environment is appropriate. For this potential to be fully realized, such structures should be reproducibly fabricated using a simple few-step process. Ideal capsules should capture the desired contents as efficiently as possible, so that little or none is wasted, and enclose these contents inside a single layer of material; they should be mechanically tough and resilient and should have stability adjustable to a wide range of conditions. Such ideal capsules should release contents in response to a variety of triggers, including mechanical perturbations and changes in the capsule environment. Many encapsulating structures are prepared via self-assembly of lipids or small surfactants, but structures made of these materials have limited strength and stability. Capsules may also be constructed using polymeric materials; this is frequently desirable because structures made of polymers are often stronger, more stable, and have a greater range of possible properties than structures made of lipids and surfactants. Capsules may be fabricated from polymeric building blocks via self-assembly of amphiphilic block copolymers,[10] layer-by-layer deposition of charged materials,[9] and emulsion polymerization.[11−13] While capsules fabricated using such techniques have many desirable attributes, no extant structure possesses in full the ideal complement of capsule characteristics.

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As an advance toward this ideal encapsulating structure, we fabricate capsules comprising a single-layer network of polymer stabilized by adsorption to colloidal particles. These capsules are made using directed self-assembly of the polymer and particles at the interfaces of emulsion droplets, which serve as templates for the capsule; this allows very high encapsulation efficiency. In their fabrication, these structures are reminiscent of colloidosomes,[14] but their properties are very different. The original realization of colloidosomes focused on capsules formed by a solid shell of sintered colloidal particles fabricated using an emulsion droplet as a template; the interstices of the particles defined the capsule permeability. By contrast, the capsules discussed here are formed by colloidal particles that adsorb at the interface of an emulsion droplet and are stabilized by a network of polymer. Their properties are dominated by the adsorbed polymer, so that these capsules are much more resilient to mechanical deformation than sintered colloidosomes. To characterize these capsules' mechanical response, we deform them using calibrated microcantilevers and describe these deformations using finite element modeling. This process is conceptually reminiscent of the method independently implemented by Dubreuil and co-workers[15] which uses a combination of interferometry and atomic force microscopy to evaluate the response of capsules made by layer-by-layer polyelectrolyte deposition; in contrast to our findings, his capsules show behavior which can be explained by standard linear elasticity theory. The very different fabrication process and mechanical response of our capsules indicates that our capsules have different structure and properties from theirs. Because we do not have an a priori determination of our capsules' structure or mechanical response, we evaluate a series of finite element models and obtain a final model that characterizes capsule mechanical properties and structure. We thereby demonstrate that these capsules are membranes inflated by osmotic pressure from internal polyelectrolyte. These capsules' mechanical response may be exploited to trigger content release as the capsule deforms under shear or loading. Furthermore, we exploit the inflating polyelectrolyte's osmotic pressure to demonstrate one of several possible nonmechanical triggers for content release by capsule deflation in response to the capsules' external environment.

Materials and Methods

Fabricating Capsules. We did all fabrication and testing at room temperature, and all materials were used as purchased unless otherwise indicated. Deionized water was used to prepare all aqueous solutions, which were without buffer and at neutral pH unless otherwise indicated. To make these capsules, we first emulsified an aqueous solution of poly-L-lysine (PLL) (0.1% w/v, MW 150−300 kD, Sigma-Aldrich) in a toluene suspension of 1.3-μm-diameter polystyrene beads with carboxyl surface groups (Interfacial Dynamics Corp., beads suspended in toluene as described by Dinsmore et al.[14]). The colloids self-assemble onto the emulsion interfaces, where PLL molecules adsorb to and lock together neighboring beads; thermal fluctuations in bead position are suppressed. The coated emulsion droplets are gently washed into octanol, which has a lower interfacial tension with water than does toluene, and then centrifuged into an aqueous solution of nonionic surfactant (TWEEN, Sigma-Aldrich, 12.5 mg/mL). This fabrication process is shown schematically in Figure 1. Once in water, capsules are highly permeable to aqueous dyes,[14] confirming that all oil has been removed. These capsules are almost always spherical, since their size and shape are determined by the initial templating emulsion droplets; capsules keep their spherical shape for 2−4 days after fabrication. Capsules in this study were deliberately fabricated to have radii of 75−200 microns because this facilitated our experiments using microcantilevers, but much smaller capsules can be fabricated using appropriately sized emulsion droplets and colloids; smaller capsules are desirable for some applications, such as drug delivery. Capsules may be filled with contents from the templating emulsion; this two-step fabrication process with an intermediate emulsion ensures that the inner phase always remains separate from the outer phase, allowing high encapsulation efficiency. The bead density on capsule surfaces varies greatly and some intact, spherical structures show large gaps between sparsely covering stationary beads, as in Figure 2; this figure indicates typical dimensions for capsules and beads in this study. This indicates that beads are held and immobilized by an adsorbed PLL network that maintains capsule integrity.

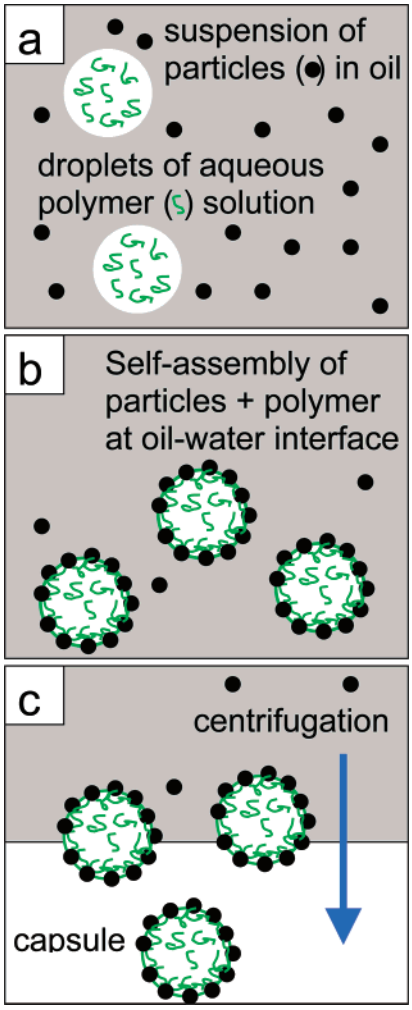

Figure 1. Schematic illustrating the fabrication process, as described in the text, and the structure of the resulting capsules.

Fabricating and Calibrating Microcantilevers: Using Microcantilevers To Deform Capsules. We measure capsules' mechanical response by indenting them with calibrated microcantilevers[16−21] under

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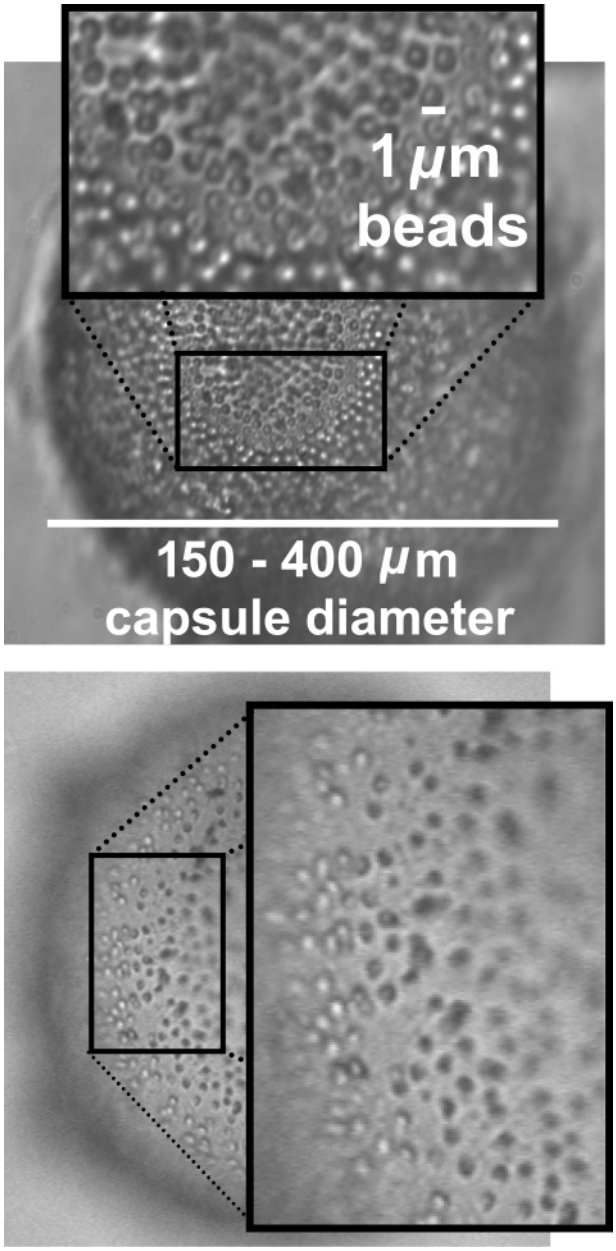

Figure 2. Capsules stabilized by polymer adsorption. The surface density of beads varies widely.

a microscope. Microcantilevers are made by pulling glass capillaries or rods in a micropipet puller, and we move them using a hydraulic micromanipulator (Narishige). The movements controlled by the micromanipulator were checked by observation under the microscope, for which magnifications were determined using reference calibration grids; micromanipulator movements were in agreement with those reported by the manufacturer. We calibrate the spring constant of each reference microcantilever by positioning the pulled tip just above a rigid straightedge mounted onto an analytical balance and then moving the microcantilever base down; the deflection of the tip of each microcantilever from its base is linear in applied force. The tips of secondary microcantilevers are bent at right angles to their bases and shaped to define the indenter geometries. Secondary microcantilevers are calibrated by pressing against reference microcantilevers and are used to deform capsules axisymmetrically. For each trial, the microcantilever tip is initially positioned to lightly pin the capsule against the rigid sample chamber wall and then the microcantilever base is advanced incrementally; the deflection of the microcantilever, and thus the force applied, is determined from the difference between the observed displacement of the tip and the known advancement of the base.

Results and Discussion

Mechanical Response of Capsules: Determination of Capsule Structure. These capsules are remarkably resilient, recovering elastically even when indented or depressed by a distance of nearly a capsule diameter. When indented by a microcantilever with a small hemispherical tip, essentially a point indenter, a deformed capsule conforms locally to the tip and elsewhere is convex with smoothly varying local curvature, as typified in parts a and b of Figure 3. Under this indenter geometry, the indentation depth appears linear in force for all capsules examined, as shown by results for two capsules, distinguished by different symbols, in Figure 4a; the different slopes of these results typify the scatter between stiff and soft capsules. We normalize the displacement and force by capsule radius because a given indentation will perturb a small structure more than a large. From this linear response, we estimate a capsule spring constant in response to point indentation, $k \approx 10^{-2}$ N/m, from which we define a modulus for the capsule, $M = k/R \approx 10^2$ Pa. This spring constant is comparable to oil−water interfacial tensions, but no such interface remains. Therefore, the elasticity must be caused by the capsule structure itself.

As an aid to inferring these capsules' structure from their mechanical response, we use finite element modeling to investigate the indentation of a water-filled elastic sphere. For such a shell axisymmetrically deformed by a point load, dimensional analysis dictates that the indentation depth, δ, depends on the indentation force or load, P, and the initial internal pressure, p, as[22]

$$\frac{\delta}{R} = f\left(\frac{P}{EtR}, \frac{PR}{Et^3}, \frac{pR}{2Et}\right) \qquad (1)$$

where t is the thickness, E the Young's modulus, and R is the radius of the shell. The first and second terms in eq 1 correspond, respectively, to the stretching and bending deformations caused by indentation. The third term is the nondimensionalized internal pressure. For an undeformed shell, the membrane tension caused by internal pressure is $S = pR/2t$, so the third term in (1) is S/E, a measure of the stretching deformation caused by internal pressure. A shell's effective stretching stiffness is $Et/(1 - \nu^2)$ and its effective bending stiffness is $Et^3/12(1 - \nu^2)$, where ν is Poisson's ratio; the bending stiffness depends more strongly on the shell thickness than does the stretching stiffness.

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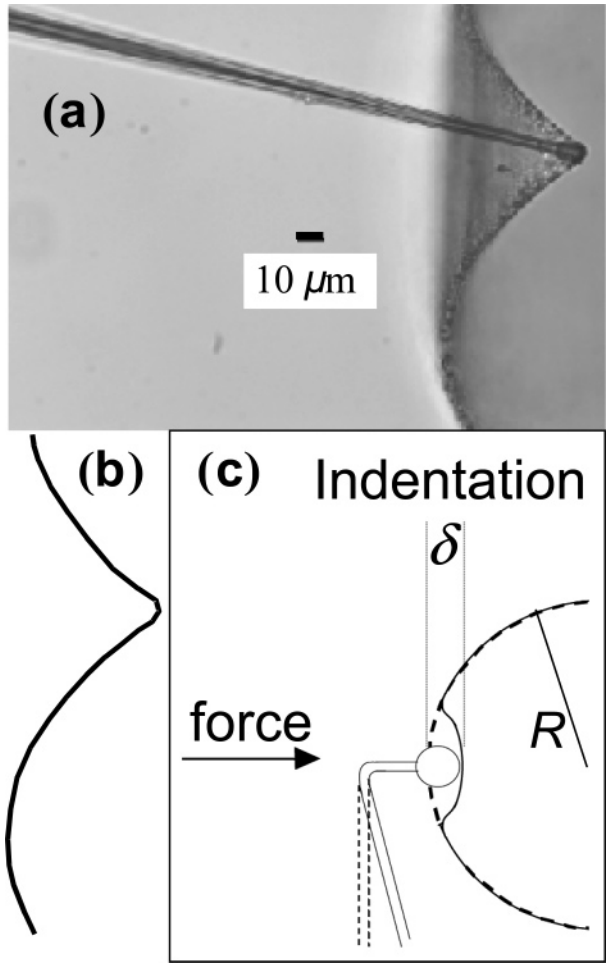

Figure 3. Capsule deforming under point indentation contrasted with indentation of an unpressurized thin elastic shell. (a) A microcantilever with a ~10 μm diameter hemispherical tip indents a 330 μm diameter capsule, which deforms to a convex geometry with smoothly varying local curvature. The capsule returns to its original spherical shape after the indenting force is released. (b) The sketch traces the capsule's deformed shape. (c) The sketch shows the deformation of an unpressurized thin elastic shell of radius *R*. Under a concentrated radial force, the shell has spherical curvature, very nearly the mirror image of the unstrained shape, over most of the deformed region. In this case, the indentation δ scales with the square of the force applied.

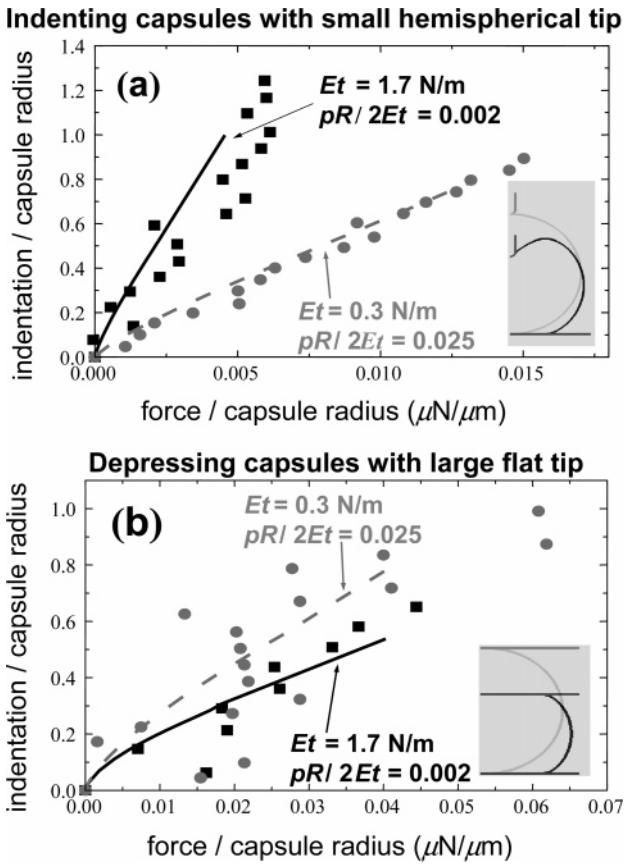

Figure 4. Indentation with (a) point and (b) large flat indenters. The deformation data (symbols) are used to fit the finite element model (lines) to determine the parameters for individual capsules; distinct symbols are used for each of these two capsules. Typical results for a soft and a stiff capsule are shown; the indentation responses for most capsules lie between these two bounds. Capsule indentations are observed with an uncertainty of less than 2 μm, and force applied is determined with an uncertainty of less than 0.3 μN for the small-tipped microcantilever and less than 2 μN for the large flat microcantilever. Capsule radii are 100−200 μm. The data and fits for two of nine capsules studied are shown. Inset sketches show finite element calculations of undeformed (gray) and deformed (black) shapes, which agree very closely with observation.

As a first attempt at modeling the structure of these capsules, we model a shell for which the bending deformations are important, so that internal pressure causes negligible stretching and shell permeability is unimportant to the deformation. Because there are geometric nonlinearities involved in the problem, an analytical solution of point indentation on a pressurized shell is not available. We therefore use numerical analysis to draw the functional form of *f*. For given shell parameter values, *f* is computed using finite element analysis with the commercial code ABAQUS.[23] The numerical model consists of 400 3-node quadratic axisymmetric elements; we assume rigid indenters and frictionless contact. For a shell with thickness 1/1000 of the radius, modeled curves describing point indentation are highly nonlinear in force. We can bring the model into better agreement with experiment by increasing the modeled shell thickness. As thickness increases, the ratio of bending to stretching stiffness increases and indentation becomes nearly linear in force; such a thick-shell model also reproduces the characteristic deformed shape of these capsules. Appropriately linear curves can be fit to experimental data to obtain a modeled shell thickness of about 1/8 of the shell radius. However, ~1 μm beads on the surface of a ~100 μm capsule do not form a thick shell, as Figure 3 shows, and capsules made with fluorescent PLL show no sign of a thick adsorbed shell. Thus, this thick-shell model is not an appropriate physical depiction of capsule structure.

From this, we infer that these capsules can be described as thin shells where $t/R \ll 1$, and we can neglect the dependence on the second term, PR/Et^3, in eq 1. An unpressurized thin shell deforms under an axisymmetric point load with a characteristic spherical indented curvature which nearly mirrors the original undeformed curvature, as illustrated in Figure 3c;[24] this indentation depth scales with the square of the force applied. We observe that the characteristic deformation of unpressurized thin shells is strikingly different from that of these capsules and therefore conclude that we must include internal pressure to correctly model their structure.

For a thin shell such that $Et^2/(12pR^2) \ll 1$, the membrane limit, the bending stiffness is negligible compared to the stretching stiffness. A membrane cannot support a load unless

(23) ABAQUS; ABAQUS Inc.: Pawtucket, RI, 1999.

constrained to stretch instead of bending when deformed; a membrane is so constrained when tensed by internal pressure. We observe that these capsules are permeable to aqueous dyes, and inferably to water; when a permeable membrane is deformed; its volume is not conserved and the internal pressure remains constant. We determine the system parameters, Et and $pR/2Et$ in eq 1, by fitting model indentations to experiment. Since the indentation depth depends on two free system parameters, fitting to point indentation data alone does not allow robust determination of the parameter values. To provide an independent set of data, microcantilevers with flat tips much larger than capsules are also used to depress capsules in a planar geometry; such data are shown in Figure 4b. When the indenter tip is much larger than the shell, the load-displacement relationship has the same dimensional dependence as before

$$\frac{\delta}{R} = g\left(\frac{P}{EtR}, \frac{pR}{2Et}\right) \tag{2}$$

but the function g differs from f. As stated above, the functional forms of both f and g are determined from extensive finite element analysis. The relationship between δ/R and P/R is measured experimentally with both point and planar indenters for each of nine capsules. For each capsule, we vary Et and $pR/2Et$ over a wide range and compute the parameter combination that best fits computed f and g to the corresponding sets of experimental data. For these capsules, fitted values range between 0.15 N/m $< Et <$ 1.7 N/m and $0.002 < pR/2Et <$ 0.06; the fitting is based on the principle of minimizing the error, so that these values have an uncertainty of less than 5%. The modeled deformations of such membranes agree well with experiment for all observed displacements, as shown for two typical capsules in Figure 4; inset sketches show the results of finite element calculations of deformed shapes, which agree very closely with observation. For these nine capsules, the average fitted parameters are $pR/2Et = 0.023$ and $Et = 0.73$N/m. We have verified that internal pressure is sufficiently large that bending effects are negligible compared to stretching, confirming that the membrane limit is valid.

To independently confirm this model, we deform other capsules, fabricated separately from the nine first studied, using a microcantilever with a thick hemispherical tip ($\sim$30 μm diameter). The data thus obtained are independent of those used to fit model parameters. Using our finite element analysis, load-displacement curves are modeled for average capsule parameters and an indenter with this geometry. These curves follow the experimental results closely, as Figure 5 shows; this further supports this model's validity.

Our model implies that most capsules are inflated by an internal pressure of 100−500 Pa. However, these water-permeable capsules cannot sustain hydrostatic pressure; this inflation must result from osmotic pressure within the capsule. Since these capsules are highly permeable to small molecules, we hypothesize that the large polyelectrolyte PLL supplies this pressure. The solution of PLL used in fabrication should produce about 2 kPa of osmotic pressure in salt-free solution.[25,26]

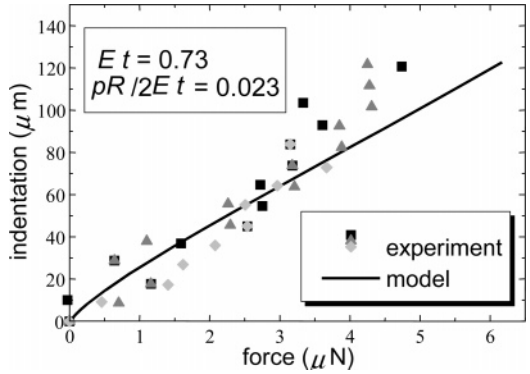

Figure 5. Results of indenting three capsules, indicated by distinct symbols, using a microcantilever with a large hemispherical tip, $\sim$30 μm in diameter. Data from these capsules were not used to fit model parameters, and these deformations, which have a different functional form from those deformations used to fit model parameters, are predicted by our model using the average fitted parameters. Deflection is determined to within less than 2 μm, and force is determined to within less than 1 μN.

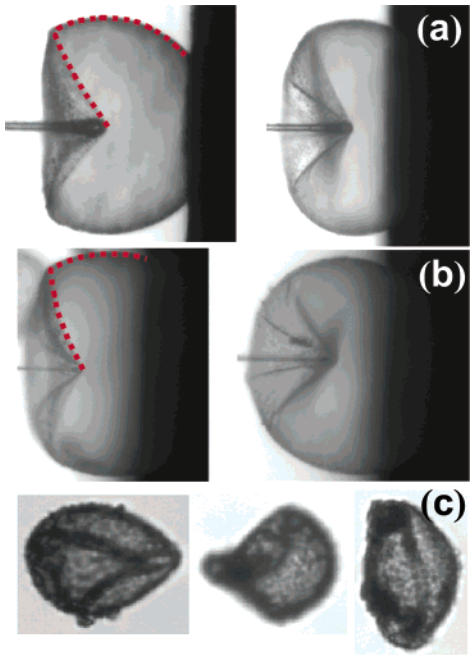

Figure 6. Partially and entirely deflated capsules. (a) Capsules made with diluted poly-L-lysine and (b) those made with undiluted poly-L-lysine and immersed in 0.025 M NaCl solution deform with near-conical indentations circumscribed by sharply bent regions, strikingly unlike the smoothly convex indentations shown in Figure 1; dashed lines are drawn as aids to the eye. These capsules have diameters $\sim$100 μm. This indentation shape and the wrinkles observed in the capsule membrane indicate that the osmotic pressure inflating these capsules has been lowered. Capsules in 1 M salt solution (c) are entirely deflated; these capsules are tens of microns in size.

However, some of the PLL is adsorbed to form the capsule membrane and does not contribute to this internal osmotic pressure; the modeled pressure is consistent with roughly 75−95% of the PLL being incorporated into the membrane.

To test that nonadsorbed PLL produces the inflating osmotic pressure, we fabricate capsules using a diluted PLL solution. Such capsules are significantly softer to point indentation and their deformed shape is not smoothly convex but instead shows a near-conical indentation circumscribed by a sharp bend, as Figure 6a shows in cross-section. This shape agrees with deformations modeled for much lower internal pressure. These observations confirm that PLL osmotic pressure inflates these capsules.

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The success of the finite element analysis in this case is striking. The colloidal beads are only 2 orders of magnitude smaller than the capsules, yet our model entirely neglects the membranes' granularity. Continuum treatment is appropriate and its success unsurprising if the membrane properties are dominated by a homogeneous layer of adsorbed PLL. Shear rheology of interfacially adsorbed PLL films yields elastic responses of about 10^{-2} to 10^{-1} N/m[27,2], agreeing in magnitude with the fitted *Et* values. These observations indicate that these are PLL capsules with the polyelectrolyte membrane, otherwise soluble in water, stabilized by adsorption to the beads. Attempts to fabricate capsules without beads were unsuccessful, indicating that such adsorption-induced cross-linking is requisite for these structures' stability.

Triggering Deflation. We can exploit PLL's properties to develop a nonmechanical release trigger to deflate capsules in response to changes in the capsule environment. In aqueous solutions, salt reduces polyelectrolyte osmotic pressure; the capsule membrane is permeable to small salt ions and aqueous counterions. Capsules in 0.025 M NaCl solution become much softer to indentation, and their deformed shapes, shown in Figure 6b, are appropriate to lowered internal pressure; these capsules were made with undiluted PLL solution but their deformed shape resembles that of capsules fabricated using diluted PLL solution, shown in Figure 6a. This indicates that the inflating osmotic pressure has been partly suppressed by the salt. In 1 M NaCl solution, capsules are entirely deflated, as shown in Figure 6c. These results suggest other possible release triggers, including pH, temperature, and solvent, upon which the charge and conformation of PLL are known to depend.[28−30] We find that capsules deflate and break at low pH but remain intact and spherical at high pH. External osmotic pressure from large molecules to which the capsule membrane is impermeable could also trigger deflation and collapse.

Modifying Capsules: Potential Applications. These novel polymer capsules are fabricated via an adaptable one-step process and are well-suited for controlled release triggered by mechanical load or shear or by changes in capsule environment. Furthermore, this fabrication pathway should be applicable to a number of cross-linking colloids and surface-active polymers. We have demonstrated this by incorporating a few gold microns-sized rods along with the polystyrene beads into capsule membranes and have also fabricated capsules using poly(diallyldimethylammonium chloride) (PDADMAC) in place of PLL. These capsules' properties and contents can be further modified by post-fabrication processing; we have demonstrated the former by layering these capsules with PDADMAC and submicron SiO_2 particles, producing a polycrystalline coating of SiO_2 particles on the outside of the capsule membrane. This technique has additional flexibility because the polymer that coats and stabilizes capsules need not be the same as the polymer that inflates capsules. The choice of inflating polymer will determine the response of the internal pressure to changing solution environments. The properties of the coating polymer and stabilizing colloids will select the modulus, compatibility, and functionality of the capsule membrane. These potentials for adaptation increase the number of functionalities and responses which these capsules can have and thereby strengthen their already-robust potential for encapsulation and controlled release.

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