# Dynamics of polymer nanocapsule buckling and collapse revealed by *in situ* liquid phase TEM

Sardar B. Alam,[1,2] Giuseppe Soligno,[1,3] Jiwoong Yang,[2,4] Karen C. Bustillo,[1] Peter Ercius,[1] Haimei Zheng,[2,5] Stephen Whitelam[1] and Emory M. Chan[1*]

[1] The Molecular Foundry, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, United States
[2] Materials Sciences Division, Lawrence Berkeley National Laboratory, Berkeley, CA 94720, United States
[3] Debye Institute for Nanomaterials Science, Utrecht University, Utrecht, 3584 CC, Netherlands
[4] Present Address: Department of Energy Science and Engineering, Daegu Gyeongbuk Institute of Science and Technology, Daegu 72988, Republic of Korea
[5] Department of Materials Science and Engineering, University of California, Berkeley, CA 94720, United States

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[*] *To whom correspondence should be addressed:* EMChan@lbl.gov

**Abstract**

Nanocapsules are hollow nanoscale shells that have applications in drug delivery, batteries, self-healing materials, and as model systems for naturally occurring shell geometries. While many nanocapsule applications require release of their cargo accompanied by their buckling and collapse, the details of this transient buckling process have not been directly observed. Here we use *in situ* liquid phase transmission electron microscopy to record the electron-irradiation-induced buckling in spherical 60-187 nm polymer capsules with 3.5 nm walls. We observe in real-time the release of aqueous cargo from these nanocapsules and their buckling into morphologies with single or multiple indentations. The *in situ* buckling of nanoscale capsules is compared to *ex situ* measurements of collapsed and micrometer-sized capsules and to Monte Carlo (MC) simulations. The shape and dynamics of the collapsing nanocapsules are consistent with MC simulations which reveal that the excessive wrinkling of nanocapsule with ultrathin walls results from their large Föppl–von Kármán numbers around $10^5$. Our experiments suggest design rules for nanocapsules with desired buckling response based on parameters such as capsule radius, wall thickness and collapse rate.

Nanocapsules[1–4] are hollow nanoparticles, 10-200 nm in diameter, that encapsulate liquids or gases inside a thin shell. Inorganic, biological, and polymeric nanocapsules have been engineered to release their contents with high spatiotemporal control.[5,6] The ability to isolate and subsequently release chemicals and materials with nanoscale precision has broad application[1,4,7] in drug delivery,[1,8] food sciences,[9] cosmetics, self-healing materials,[10,11] pressure sensors,[12] mechanical actuators,[13] battery electrodes,[14–16] and carbon capture.[17,18] In these applications, cargo release can be stimulated via shifts in pH[19] or osmotic pressure,[12] or by exposure to chemicals,[20] heat,[21–23] light,[22–24] magnetic fields,[25] shear flow,[26] ultrasound[27] or mechanical force.[11,28] Such triggering relies on the fact that the thin walls of the nanocapsules make them susceptible to buckling and collapse under compressive strain. This buckling is driven by the conversion of the in-plane energy required to stretch or compress the shell membrane into energy used to bend the membrane out-of-plane.[29,30] As a result, a small amount of in-plane shell compression can lead to large and abrupt distortions of the nanocapsule morphology. Since this mechanical behavior can strongly influence the rate and direction at which the nanocapsules release cargo, there is a strong application-driven need to understand the buckling of capsules at nanometer length scales.

Predicting the buckling behavior of spherical shells is not trivial. Depending on a capsule's dimensions, composition, defects, and rate of cargo release, a capsule can buckle into a range of non-spherical geometries,[31–33] from bowl-shaped colloids with single indentations (Figure 1ef), to nanocapsules with multiple indentations (Figure 1c, Figure S3), crumpled

geometries (Figure S2), or flat disks. This buckling can occur via multiple pathways, even ones that ultimately produce the same final morphology.[31–36]

This study focuses on buckling pathways driven by volume loss, which is initiated by leakage of cargo through ruptures or pores in nanocapsule walls. The use of controlled volume loss[30,31,33] as the mode for collapse, rather than external pressure, is beneficial since chemical delivery based on leakage is more relevant for shells found in nature[37] and practical applications.[5] Such leakage of liquid leads to inward-directed capillary forces that drive buckling[33,38,39] (see Supporting Information Section 3). Initially this interfacial capillary pressure causes the shell to contract isotopically while retaining its spherical shape, thus increasing its in-plane stretching energy. When the pressure difference across the shell exceeds a critical pressure[29,30](defined in the SI Section 3), the shell undergoes buckling instability to trade costly in-plane stretching energy for bending energy.[30–32] According to classical shell buckling theory,[29,30] the critical pressure difference required to indent or buckle shells is directly proportional to the ratio $h/R$, where $h$ is the membrane or wall thickness and $R$ is the capsule radius (illustrated in Figure 2c). Capsules with thinner walls and larger diameters, i.e., low $h/R$, are more susceptible to buckling. The final shape of the capsule depends, in addition to the ratio $h/R$, on the relative volume loss, deformation rate, and the dimensionless Föppl–von Kármán number ($\gamma$).[31] $\gamma$ is proportional to $(R/h)^2$ and to the ratio of the in-plane stretching and out-of-plane bending energies of the shell; thus, it summarizes the elastic response of the capsule (see SI Section 4).[31] Preexisting inhomogeneity of capsule walls and defects will also reduce the critical pressure difference that drives buckling.[34,35]

The ability to observe the transient stages of buckling in real-time[13,16,20,22,33,34,40,37,41,42] would improve our understanding of this complex process and its dependence on the structural parameters listed above. Such *in situ* studies could inform the design of capsules immune to premature release and with cargo release mechanisms optimized for targeted applications. Real-time imaging of nanocapsule collapse could in principle reveal relationships between the buckling process and key physical parameters such as shell defects, the dynamic morphology of an evolving capsule, and the rate and spatial distribution of cargo release. The resulting understanding could also inform strategies to select buckling pathways that lead to desired non-spherical morphologies, such as bowl shaped nanocapsules[43] that increase cellular intake[44] and promote colloidal assembly.[43,45,46]

Due to the small dimensions of the nanocapsules, previous investigations into the deformation of nanoscale shells by volume loss have largely been limited to examining the final buckled geometries with *ex situ* electron microscopy,[47,48] theoretical studies,[30,32] and simulations.[31] There are few experimental studies that capture the short-lived intermediate stages of buckling nanocapsules and are limited to dry hollow capsules.[16,41,42] A key limiting factor is that *in situ* imaging methods must be able to trigger and simultaneously record the buckling process in real-time with resolution sufficient to capture nanoscale features such as defects on the capsules and the indentations formed during buckling. *In situ* TEM investigations of buckling have used mechanical indentation to probe dry hollow shells,[16,41,42] but many applications require shells that encapsulate or operate in liquid. With recent advancements in liquid phase *in situ* TEM,[49,50] the dynamics of capsules[51–53] and other soft colloids[54–56] can now be observed with high spatial and temporal resolution. If the appropriate liquid cell and triggering mechanism were

developed, *in situ* TEM could be exploited to record the complete dynamics of nanocapsule collapse.

Here, we leverage the high spatial resolution of *in situ* liquid phase TEM to record the entire buckling process of polymer nanocapsules from initial leakage of liquid cargo to the final collapse of capsules while capturing the intermediate buckling states. We synthesized surfactant-templated polymeric nanocapsules[57,58] and encapsulated them in graphene liquid cells[59,60] to isolate the capsules from the vacuum inside the TEM column . Buckling was initiated by irradiating the nanocapsules with an electron dose rate much higher than necessary for imaging. Unlike mechanically driven deformations,[16,28,41,42] the electron beam is a contactless trigger that can degrade the polymer walls of the nanocapsule and is analogous to other remote triggers like heat[21,22] or light.[24] Using this *in situ* TEM approach, we recorded different buckling morphologies of nanocapsules and compare them to *ex situ* experiments, microscale capsules, and Monte Carlo (MC) simulations. We mined these data to determine buckling pathways and investigate how they are influenced by factors such as collapse rate, $h/R$, $\gamma$, and imperfections in the shell. MC simulations are used to understand how stretching and bending energies drive collapse pathways. We compare the buckling of nanoscale capsules to simulation results and the buckling of microscale capsules. Finally, we use these observations to formulate design principles for nanocapsules targeted for controlled release applications.

## Results and discussion

**Nanocapsule synthesis and characterization.** Nanocapsules based on copolymers of butyl methacrylate (BMA), tert-butyl methacrylate (t-BMA), and ethylene glycol dimethacrylate (EGDMA) were synthesized using cationic surfactant vesicles as scaffolds.[57,58] Methacrylate monomers were loaded within the bilayer of surfactant vesicles comprised of sodium dodecylbenzenesulfonate (SDBS) and cetyltrimethylammonium p-toluenesulfonate (CTAT) surfactants mixed at 80:20 or 20:80 ratios. Although these vesicles exhibited polydisperse size distribution with diameters ranging from 10 nm to 100 μm, the size distributions could be controlled via extrusion through porous membranes[57,58,61] – a primary advantage of this synthetic approach. Monomer-loaded vesicles were extruded through polycarbonate membranes with 100 nm pores seven or fifteen times to obtain a monodisperse population of vesicles with diameters ranging from 50 to 200 nm, as illustrated by size histograms (Figure 1a) acquired with dynamic light scattering (DLS). Subsequent photoinitator-mediated photopolymerization crosslinked the monomers inside the bilayer, thereby forming robust polymer capsules (Figure 1bcd). After purification to remove the surfactant template and residual monomer, the nanocapsules were loaded in graphene liquid cells and were imaged using either a JEOL 2100 TEM or Thermo Scientific Themis TEM operating at 200 and 300 kV, respectively. TEM imaging revealed nanocapsule shell thicknesses of 1.0-3.5 nm (Figure 1bcd) for samples extruded seven or fifteen times through the polycarbonate film. For *in situ* buckling experiments, the polymer nanocapsules were loaded with lead (II) nitrate during vesicle formation to enhance image contrast and facilitate tracking of released cargo. Details of the polymer capsule synthesis, graphene liquid cell assembly and TEM imaging are presented in the Supporting Information.

To compare nanocapsules with capsules having thicker shells and much larger diameters, we also polymerized capsules without first extruding the surfactant templates. This approach produced capsules with a large size variation (Figure 1ef, Figure S4), allowing investigation of polymer capsule sizes that range from tens of nanometers to tens of micrometers. Capsules larger than 400 nm, however, could not be successfully loaded in graphene liquid cells because their large diameters resulted in the rupture of the graphene sheets (Figure 1g).

***In situ* initiation and observation of buckling.** To understand the pathways for buckling, we investigated the dynamics of nanocapsule collapse via analysis of *in situ* TEM image sequences. Initially the polymer nanocapsules remained stable at moderate electron dose rate of less than 200 $e^-/Å^2s$ at an accelerating voltage of 200 kV. We did not observe any moving liquid interfaces or formation of gas bubbles which leaves open the possibility that the region surrounding the nanocapsules may not be fully hydrated. When the electron dose rate was increased to ~1000 $e^-/Å^2s$ (corresponding to a current density of ~250 $pA/cm^2$ measured at the fluorescent screen of the TEM), the nanocapsules were observed to abruptly collapse (Figure 2 and Supplemental Movies), releasing the lead nitrate solution encapsulated in the colloids. For all *in situ* experiments (Figure 2 and 3), the ejection of liquid and rapid loss of volume is accompanied by the start of buckling. The correlation between the leakage of liquid from the capsules and buckling of capsules indicates that inward-directed capillary forces drive the buckling process (Supporting Information Section 3). The high-intensity e-beam presumably damages the polymer shell of the capsules and leads to formation of pores or ruptures that allow liquid cargo to escape (similar to buckling triggered by stimuli such as light and heat). Thus, we were able to leverage e-beam irradiation to induce buckling during *in situ* experiments.

Figure 2a and Supporting Movie 1 show the dynamics of buckling and collapse of a polymer nanocapsule with a 3.4 nm thick shell and 150 nm diameter. Initially the nanocapsule in Figure 2a (SI Movie 1) remains stable for the first 80 s of the recording (the time $t = 0$ s in these image sequences indicates the start of the recording and not the initiation of electron irradiation). Subsequently, small droplets 12-25 nm in diameter begin leaking from the capsule at 82 s, followed by the ejection of a larger liquid jet and sudden appearance of three large indentations at 86.3 s. The onset of buckling is followed by further release of aqueous cargo as the indentations become deeper. As the highly scattering lead (II) nitrate solution escapes the buckling capsule, the interior of the capsule became brighter with higher grey values. As the polymer membrane collapses, the indentations expand and ultimately result in the formation of a Y- or H-shape pattern (see examples in SI Figure S3) commonly observed for the buckling of macroscopic elastic shells.

The 187 nm diameter capsule in Figure 2b and SI Movie 2 behaves similarly to the capsule highlighted in Figure 2a, although the final morphologies of the two capsules differ. At 40 s, droplets (ca. 20 nm) begin leaking from the capsule, followed by substantial leakage of cargo and the sudden appearance of several new indentations at 41.2 s. One indentation (labeled II in Figure 2b) grows at the expense of the other indentations, resulting in a nanocapsule equilibrating to a bowl-shaped morphology with a single indentation (46.3 s).

**Evolution of buckling morphologies.** The differing final shapes of the nanocapsules in Figure 2a and Figure 2b suggest that they have distinct buckling pathways. To understand these pathways and their relationship to nanocapsule structure, we focused our analysis on larger indentations (i.e., those with depths comparable to the capsule radius $R$), since these features

grow and define the final buckled morphology. In Figure 2a, deep indentations greater than 50 nm instantaneously appear at 86.3 s (indentations II and III; also see Figure 2c). After their sudden appearance, these large indentations grow and later either slightly decrease (II) or grow at a slower rate (III) to reach a final depth $H$ of approximately 70 nm. In addition to II and III, indentations I, IV and V also grow to depth of ca. 30 to 40 nm leading to final deformed capsules with H-shaped ridges and multiple indentations.

As in Figure 2a, the buckling of the ca. 187 nm nanocapsule in Figure 2b and Movie 2 starts with the appearance of multiple large indentations. In contrast to the capsule in Figure 2a, the indentations in Figure 2b grow into a single indentation. After initiation of buckling, two large indentations (II and III) with respective depths $H$ of 58 and 39 nm dominate the morphology of the capsule by $t$ = 42.9 s. As the buckling proceeds, these indentations continue to grow in parallel at different rates: 25 nm/s for indentation II and 11.5 nm/s for indentation III. By $t$ = 44.4 s, indentation II is 105 nm deep while III is 58 nm. After $t$ = 44.8 s, however, the deeper indentation II grows further but at the expense of indentation III, which gets shallower. Indentation II continues to grow past $t$ = 45.2 s, but at a slower rate (6 nm/s). Meanwhile the depth of indentation III decreases at a much faster rate of -45 nm/s until it disappears. This process yields a final bowl-shaped, collapsed geometry with only one large indentation (II) at $t$= 46.3 s. The collapse of the nanocapsule in Figure 2b takes 6.6 s, 1.5-fold slower than the similarly sized capsule in Figure 2a. The normalized volume loss $\Delta V/V_o$ of 0.6 can be used in conjunction with TEM images to calculate a relatively high $\gamma$ of ~ 1.1 x $10^5$ (see SI Section 4 for details on calculating $\gamma$ from buckled geometries). This dimensionless $\gamma$ value will be used in

later sections to compare the behavior of nanocapsules with varying structural properties and to define capsules in MC simulations

In some cases, nanocapsule buckling can proceed with only one indentation nucleating and growing into a final morphology that resembles an excessively wrinkled and deformed bowl.[31,33] Figure 3bcd and corresponding Movies 4, 5 and 6 are examples of such events. Since γ scales with $(R/h)^2$, the capsules in Figure 3 and Figure 4 with diameters ranging from 60 to 85 nm should have a smaller γ of the order of $10^4$ compared to nanocapsule in Figure 2b ($2R$ = 187 nm, $\gamma = 1.1 \times 10^5$).

In Figure 3bdc, the nanocapsules do not collapse into a symmetric bowl shape with a circular or smooth rim. In contrast to the examples in Figure 1e and 1f, the final collapsed bowl morphologies of the nanocapsules in Figure 3bdc have excessive wrinkling, with asymmetrical or polygonal shaped rims. For most microscale polymer capsules, a polygonal rim is reported to appear post-buckling from a bowl-shaped capsule with circular rim.[33,62] However, we observe a direct transition from a spherical capsule to the asymmetric, globally deformed bowl shapes shown in Figure 3bdc, with excessive wrinkles and non-circular rims. This direct transition to asymmetric single indentation has been reported by numerical simulations[63] for capsules with large γ values but experimental observations have thus far been limited.

**Rate and timing of cargo release.** The volumetric rate at which the nanocapsules release their cargo is an important parameter for controlled release applications. We observe an approximately linear relationship between the volumetric rate of cargo release and the size of the capsules (Figure 4b). The larger, 150-187 nm diameter capsules in Figure 2 release their cargo at a higher volumetric rate compared to the smaller, 60-85 nm capsules in Figure 3. For example,

the fastest release is recorded for the capsule in Figure 2b at $5.2 \times 10^5$ nm$^3$/s, which is an order of magnitude faster than the smallest capsule in Figure 3a with a rate of $3.8 \times 10^4$ nm$^3$/s. However, when we normalize the collapse rates by initial volume (Figure 4a), the larger capsules do not have a statistically higher normalized release rate compared to smaller capsules. The insensitivity of the normalized collapse rate to nanocapsule volume means that, for nanocapsule applications, a given cargo delivery rate can be achieved using a single capsule or multiple smaller capsules with the same overall volume.

In the case of nanocapsules with $R < 45$ nm and similar $h/R$ (and hence $\gamma$), the capsules that take longer than the average time of 4.2 s to collapse (shown in Figure 4c) have a single indentation while those with shorter times generally collapse with multiple indentations, with Figure 3c as the exception. In Figure 4c, the dependence of buckling response on $\gamma$ can also be seen; the largest capsule still starts with multiple indentations despite taking the longest time to collapse.

**Effect of preexisting indentations/dimples.** Previous reports have suggested that shallow defects in nanocapsule walls can drastically reduce the critical pressure for initiating buckling[30] and affect buckling pathways.[34,35] The nanocapsules in Figure 2 and Figure 3 have four to seven pre-existing indentations that are comparable in depth to the shell thickness (about 3-5 nm). However, we do not observe any correlation between the number of pre-existing indentations and the start time of buckling or the rate of cargo release from the capsules (Figure 4b). Furthermore, these indentations do not appear to dictate the collapse of the nanocapsules; we observed that major indentations do not originate from preexisting shallow indentations. For example, capsules in Figure 2ab already have small indentations (e.g., indentation I in both

cases) at the onset of imaging, but during the e-beam induced collapse, indentation I does not grow. Instead, large new indentations (indentation II and III) suddenly appear. These results could suggest that, relevant to larger capsules, the e-beam triggered buckling process of nanocapsules is more tolerant to the presence of pre-existing dimples and defects.

***Ex situ* buckling & regimes of capsule collapse.** In order to develop a more complete understanding of how the initial nanocapsule structure can result in different collapse morphologies, we imaged *ex situ* a library of larger capsules across a range of shell thicknesses $h$ and radii $R$ (Figure 5). Polydisperse populations of *ex situ* samples, 50 nm to 24 μm in diameter (Figure 5a), were produced by omitting extrusion from some synthetic protocols. For *ex situ* experiments, nanocapsule collapse was initiated by first drying the samples in air and later depressurizing samples on an open TEM grid in a vacuum desiccator (see SI Methods). In addition to allowing analysis of a broader size range of nanocapsules (larger capsules breach the graphene cells), *ex situ* analysis has the added benefit of facilitating comparison of *in situ* TEM buckling of capsules driven by e-beam with more prevalent evaporation-driven collapse. Since critical pressure and γ depend on $h$ and $R$, we investigated the dependence of buckling response on $h$ and $R$.

The phase diagram and representative micrographs in Figure 5a illustrate three distinct regimes of collapse and establish that the ratio $h/R$ can be used to predict the buckling shape for a capsule with a given chemical composition. When $h > R/5$ (Regime I), polymer capsules retain their spherical shape and do not buckle or collapse. This phase boundary provides an upper limit of $h/R$ for applications where buckling is preferred and also provides a lower limit for the synthesis of stable shells. The linear fit for unbuckled stable capsules in Figure 5a (green

pentagons) gives $h \approx R/1.6$. This is comparable to the limit $h > R/4.34$ limit reported for silica/siloxane shells,[47] and is significantly larger than the limit of $h > R/16$ reported for polydopamine microcapsules[33] dried by evaporation.

When $h < R/5$, nanocapsules collapse in two regimes (II, III) that we distinguish by the number of indentations in the final product. In Regime II, when $R < 100$ nm and $h < 10$ nm, nanocapsules are crumpled or exhibit multiple indentations. The clear boundaries for Regime II are observed irrespective of the process used to initiate collapse *i.e.*, by *in-situ* e-beam exposure or *ex-situ* vacuum. This indicates that smaller capsules collapse at higher deformation rates and are trapped in various metastable states. However, in Regime III, characterized by larger microscale capsules (100 nm $< R <$ 10 μm) with thicker shells ($h >$ 50 nm), only single indentations are observed. For these samples, deformation is likely slow and hence more tuned for morphological control.

Among capsules with single indentations, the depth of the indentation $H$ and the relative change in volume of the buckled capsules were observed to increase with decreasing $h/R$ (Figure 5b). This relationship is significant for applications such as drug delivery because it shows that, by tuning $h$ and $R$ of a nano- or microcapsule (assuming an identical chemical composition, elastic modulus, and deformation rate), one can program the final capsule state and thus the exact volumetric dose of cargo. To relate these properties to the mechanical characteristics of the capsules, we calculated their Föppl–von Kármán numbers ($\gamma$) from the relative change in volume $V$ of the buckled capsules ($\Delta V/V_o$, where $\Delta V$ is the change in volume and $V_o$ is the initial capsule volume; see SI Section 4). For capsules with circular bowl rims, $\gamma$ ranges from ca. 8000 for microcapsules with large volume loss to 80 for the lowest volume change in Figure 5b. These

□ values are several orders of magnitude smaller than the nanocapsule in Figure 2b; this difference is reflected in the smooth rims and wrinkle-free shapes for the capsules with lower □ values. The examples in Figure 5b demonstrate that capsules with $h/R > 0.1$ can be tuned to have smooth, circular-rim bowls with desired depth $H$ and precisely defined cavity volumes, which may be useful for colloidal assembly.[45,46]

TEM tilt series shown in Figure 6 show two examples of capsules with $\Delta V/V_o \sim 0.9$ but with different morphologies. In both cases, the capsules are fully collapsed, which is common when the capsules snap under mechanical stress.[30] However, our data illustrate that when $h/R$ is near or below 0.1, even volume-loss driven buckling can lead to such fully collapsed shapes. The $h/R$ ratio can further help us predict if the fully collapsed bowl will have a circular rim or a polygonal rim and a globally deformed capsule. The capsule in Figure 6a has $h/R = 0.12$ and □ ~ 5000 and results in a completely collapsed bowl shape. Similarly, the capsule in Figure 6b, with $h/R = 0.05$ and an estimated □ ~ $10^4$ appears to have undergone post-buckling with a polygonal rim with three to eight vertices. Further examples of globally deformed capsules in Figure S5def and Figure S6 all have $h/R < 0.1$, comparable to the *in situ* TEM examples in Figure 2 and 3. This sets a lower limit of $h/R > 0.1$ for creating capsules with well-defined bowl shapes where bending energy is predominantly confined to the circular rim.

**Interpretation of buckling pathways via comparison with Monte Carlo simulations.** To gain further insight into how the energetics of deforming nanocapsules influence their buckling pathways, we performed Monte Carlo simulations of the collapse of a spherical elastic shell using methods derived from Vliegenthart and Gompper.[31] Our model simulates buckling by linking the probability of deforming a closed spherical mesh of 6000 vertices to the energy

required for in-plane stretching/compression and out-of-plane bending (complete simulation methods are detailed in the Supporting Information). The elastic response of the single-layer mesh is set through its γ parameter, which encapsulates information about Young's modulus, bending rigidity, and ratio *R/h* of the capsule. The use of the dimensionless parameter γ allows us to compare simulation results to our experimental data, because γ can be extracted from TEM images. Membranes with γ values of $2.67 \times 10^3$ and $2.67 \times 10^5$ were simulated to correspond roughly to the microscale capsules in Figure 5b and the nanoscale capsules in Figure 2, respectively. The simulated buckling of the elastic grid was induced by changing the volume $V$ of the elastic grids at a compression rate $\delta V$ per MC move. Three different volumetric compression rates $\delta V$ of $10^{-8}$, $10^{-9}$, and $10^{-10}$ (expressed in cubic units of length, where the radius of the initial spherical mesh is one length unit) were simulated for both values of  to understand the effect of deformation rate on the buckling process.

Figure 7 (and SI Movies 7,8,9 and 10) illustrates that varying γ and $\delta V$ result in a range of simulated capsule morphologies for a given reduction in volume. Simulation predictions are consistent with experimental results in which large γ (Figure 2a) and/or large $\delta V$ lead to the emergence of multiple large indentations and wrinkled shell surfaces. However, simulations suggest that, given sufficient time to relax (i.e., small $\delta V$), the capsules with low γ will relax to a state with a single indentation. Consistent with experiments (Figure 2bd) and previous simulation results,[31] Figure 7 shows that the number of indentations decreases over time, via a process in which small indentations disappear at the expense of larger indentations. Though recent MC simulations by Vliegenthart and Gompper[31] and our simulations both show relaxation via an

Oswald ripening-like mechanism, full relaxation into single indentations for γ values of $10^5$ is not observed in either set of simulations. Our experimental data demonstrates that even for large γ ~ $10^5$ (Figure 2bd), a nanoscale capsule can relax into a single indentation via an Ostwald-ripening-like process. This transition from multiple indentations to a single one in Figure 2b also indicates that the compression rate due to capillary forces from cargo leakage is sufficiently slow to allow full relaxation.

The behavior of the indentations, and thus buckling, can be explained by analyzing the bending energy $E_b$, stretching energy $E_s$, and the total energy $E = E_b + E_s$, of the simulated nanocapsules as shown in Figure 8 for each simulation illustrated in Figure 7. We follow these energies across different stages of volume loss (i.e., MC steps), at different normalized volumes $V^* = V/V_o$, where $V_o$ is the initial volume.

For a given $V^*$, the simulation with the lowest total energy $E$ (Figure 8a) is the nanocapsule with only one indentation, pictured in Figure 7a (and SI Movie 7). This low energy configuration corresponds to the nanocapsule with the smallest γ and $\delta V$. Single-indentation structures are understandably found at energy minima (*i.e.,* their ground or equilibrium state), because all elastic energy is confined to the circular rim of the indentation. When the compression rate is sufficiently slow at low γ (~$10^3$), the nanocapsule has time to equilibrate to this minimum-energy configuration even when transient fluctuations distort the membrane. All of the larger microscale capsules in Figure 5 fall in this low γ, slow $\delta V$ regime, which we postulate is due to the slow volume loss associated with evaporation. This observation highlights that the single bowl shape is the most reproducible and well-controlled morphology.

Simulations of nanocapsules with multiple indentations, observed at higher γ (~ $10^5$, signifying greater *R/h* or a more flexible membrane), have a greater proportion of their surface area devoted to high-energy bends and thus have greater total energy *E* at a given *V** (see Figure 8d and Movie 10). At large δ*V* (Figure 8cf), the elastic membrane is forced away from equilibrium during buckling and remains trapped in a metastable, high-energy configuration that corresponds to shapes with many indentations. For a given *V** and γ, MC simulations show that capsules buckling with larger δ*V* have more indentations and wrinkles compared to simulations with slower compression rates. These simulation results agree with our experimental findings in Figure 2 and 3 in which nanocapsule buckling is accompanied by excessive wrinkling of the surface. This correlation is also consistent with *in situ* TEM data in Figure 4 where nanocapsules with similar γ generally collapse with multiple indentations if their collapse time is below average (4.2 s). Even with a smaller γ of $10^3$, a larger compression rate leads to larger elastic energies with the system unable to relax or ripen before it is compressed further (Figure 8bc, Movie 8 and 9).

The temporal evolution of $E_b$ and $E_s$ provides insight into the propensity of nanocapsules to buckle and their affinity for specific pathways. For most simulations, the stretching energy increases during the initial stages of volume reduction while the bending energy remains nearly constant. At this early stage, the elastic grid maintains an approximately spherical shape while shrinking in volume. As the volume reduction continues, buckling will initiate when indenting the nanocapsule is energetically more favorable than compressing it isotropically (e.g., at *V** ~ 0.8 in Figure 8b, Movie 8). This transition is marked by the abrupt rise in bending energy while the stretching energy drops dramatically. This buckling point shifts to lower reduced volumes

(higher $V^*$) for higher γ values and slower compression rates (e.g., compare Figure 8c with Figure 8d and Movie 9 with Movie 10). This trend is consistent with *in situ* measurements of buckling of capsules in Figure 2 and 3; at $\gamma \sim 10^5$ and relatively slow compression rates; we do not observe appreciable isotropic shrinkage of the nanocapsules before the onset of buckling.

This agreement between simulation and experiment implies that capsules with larger γ will buckle more readily with small amounts of compression or deformation, highlighting the challenges in creating uniform buckled geometries for shells with ultrathin walls. These insights from experiment and simulation suggest that nanocapsule applications that require uniform buckled morphologies should apply slow deformation rates to nanocapsules with small radii or thicker walls (i.e., low γ). The fact that the simulations accurately predict buckling of nanoscale capsules implies that buckling pathways observed for microscale capsules are mostly conserved when scaling hollow shells down to nanometer length scales.

## Conclusions

The buckling and collapse of 60-187 nm polymer capsules were recorded in real-time using *in situ* liquid phase TEM in graphene liquid cells, with the electron beam used as a contactless triggering probe. Similar to micro- and macroscopic shells, nanocapsules were observed to buckle into collapsed structures with single or multiple indentations. Using both *in situ* and *ex situ* data to build a phase diagram of buckling outcomes over multi-dimensional experimental space, we show that buckling pathways are determined predominantly by $h/R$ (the ratio of wall thickness to capsule radius), the Föppl–von Kármán number γ, and the compression

rate $\delta V$. The dependence of buckling mechanisms on the dimensionless $h/R$ rather than capsule size ($R$), means that nanocapsule buckling is largely consistent with models developed for microscale capsules. As predicted by MC simulations, a combination of low $\gamma$ and $\delta V$ give rise to nanocapsules with single indentations, which are the lowest energy configuration. In contrast, large $\gamma$ or $\delta V$ produce multiple indentations that are kinetically trapped. *In situ* recordings demonstrate that capsules with relatively high $\gamma$ (~$10^5$) that initially nucleate multiple indentations can still relax to an energetically favorable state with a single indentation at sufficiently slow compression rates and time. This Ostwald ripening-like process has been predicted only at lower $\gamma$ but is shown experimentally in nanocapsules at $\gamma$ ~$10^5$.

Our investigations revealed several design principles that can guide the development of nanocapsules targeted towards the triggered release applications. First, polymer nanocapsules provide a mechanism for dispensing precise, atto- to zeptoliter volumes of solutions that can be tuned by varying the dimensions ($R$, $h$) or mechanical properties ($\gamma$) of the nanocapsules. Decreasing the $h/R$ ratio leads to deeper bowl-shaped indentations. Buckling into single-indentation bowl shapes, which can be accessed at low $\gamma$ and $\delta V$, is preferable due to the higher uniformity of the end product. Nanocapsules with low $\gamma$ are also more stable and less prone to buckling, whereas capsules with high $\gamma$ will buckle with only light compression ($\Delta V/V_o$), which may be preferred for some applications. Another important design rule is that the volumetric rate of cargo release is roughly proportional to the nanocapsule volume. An interesting consequence of this rule is that the size of individual nanocapsules and their polydispersity are not critical parameters as long as the total internal volume of nanocapsules is conserved. Also relevant for production of nanocapsules is the fact that imperfections in nanocapsules, such as

multiple pre-existing indentations, do not appear to affect the rate or onset of buckling, which is not necessarily true for micro- and macroscale capsules.

Finally, this work demonstrates the value of *in situ* TEM for studying complex dynamics in soft materials like liposomes[51,53] or synthetic nanocapsules.[52] For instance, *in situ* TEM can help to optimize the buckling of polymer nanocapsules in more complex situations like presence of flow fields, viscous or nanoparticle- containing cargo, and heterogeneous composition of capsule walls. Furthermore, the controlled delivery of reagents from polymer nanocapsules, triggered by electron irradiation or other remote stimuli, provides a mechanism for initiating reactions with high spatiotemporal control in confined geometries such as TEM liquid cells.[51] This nanocapsule-based strategy could provide an alternative to complex pumps and valves in liquid cells[64] and could enable high-throughput nanoscale imaging of thousands of independent reactions (e.g., nanocrystal growth) confined on single substrate.

**Supporting Information:** Supporting Movies 1-10. Methods, theory, MC simulation setup and additional images of buckled capsules.

## Conflict of Interest

The authors declare no competing interest.


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## References

(1) Tanner, P.; Baumann, P.; Enea, R.; Onaca, O.; Palivan, C.; Meier, W. Polymeric Vesicles: From Drug Carriers to Nanoreactors and Artificial Organelles. *Acc. Chem. Res.* **2011**, *44* (10), 1039–1049.
(2) W. Peters, R. J. R.; Louzao, I.; Hest, J. C. M. van. From Polymeric Nanoreactors to Artificial Organelles. *Chem. Sci.* **2012**, *3* (2), 335–342.
(3) Gaitzsch, J.; Huang, X.; Voit, B. Engineering Functional Polymer Capsules toward Smart Nanoreactors. *Chem. Rev.* **2016**, *116* (3), 1053–1093.
(4) C. Bentz, K.; A. Savin, D. Hollow Polymer Nanocapsules: Synthesis, Properties, and Applications. *Polym. Chem.* **2018**, *9* (16), 2059–2081.
(5) Esser-Kahn, A. P.; Odom, S. A.; Sottos, N. R.; White, S. R.; Moore, J. S. Triggered Release from Polymer Capsules. *Macromolecules* **2011**, *44* (14), 5539–5553.
(6) Che, H.; van Hest, J. C. M. Stimuli-Responsive Polymersomes and Nanoreactors. *J. Mater. Chem. B* **2016**, *4* (27), 4632–4647.
(7) Amstad, E. (first). Capsules: Their Past and Opportunities for Their Future. *ACS Macro Lett.* **2017**, *6* (8), 841–847.
(8) Castro, K. C. de; Costa, J. M.; Campos, M. G. N. Drug-Loaded Polymeric Nanoparticles: A Review. *Int. J. Polym. Mater. Polym. Biomater.* **2022**, *71* (1), 1–13.
(9) Ameta, S. K.; Rai, A. K.; Hiran, D.; Ameta, R.; Ameta, S. C. Use of Nanomaterials in Food Science. *Biog. Nano-Part. Their Use Agro-Ecosyst.* **2020**, 457–488.
(10) Zhao, Y.; Fickert, J.; Landfester, K.; Crespy, D. Encapsulation of Self-Healing Agents in Polymer Nanocapsules. *Small* **2012**, *8* (19), 2954–2958.
(11) Souza, L.; Al-Tabbaa, A. Microfluidic Fabrication of Microcapsules Tailored for Self-Healing in Cementitious Materials. *Constr. Build. Mater.* **2018**, *184*, 713–722.
(12) Kim, S.-H.; Lee, T. Y.; Lee, S. S. Osmocapsules for Direct Measurement of Osmotic Strength. *Small* **2014**, *10* (6), 1155–1162.
(13) Jampani, V. S. R.; Mulder, D. J.; Sousa, K. R. D.; Gélébart, A.-H.; Lagerwall, J. P. F.; Schenning, A. P. H. J. Micrometer-Scale Porous Buckling Shell Actuators Based on Liquid Crystal Networks. *Adv. Funct. Mater.* **2018**, *28* (31), 1801209.
(14) Wang, J.; Cui, Y.; Wang, D. Hollow Multishelled Structures Revive High Energy Density Batteries. *Nanoscale Horiz.* **2020**, *5* (9), 1287–1292.
(15) Wang, J.; Tang, H.; Zhang, L.; Ren, H.; Yu, R.; Jin, Q.; Qi, J.; Mao, D.; Yang, M.; Wang, Y.; Liu, P.; Zhang, Y.; Wen, Y.; Gu, L.; Ma, G.; Su, Z.; Tang, Z.; Zhao, H.;

Wang, D. Multi-Shelled Metal Oxides Prepared via an Anion-Adsorption Mechanism for Lithium-Ion Batteries. *Nat. Energy* **2016**, *1* (5), 1–9.
(16) Jin, Y.; Li, S.; Kushima, A.; Zheng, X.; Sun, Y.; Xie, J.; Sun, J.; Xue, W.; Zhou, G.; Wu, J.; Shi, F.; Zhang, R.; Zhu, Z.; So, K.; Cui, Y.; Li, J. Self-Healing SEI Enables Full-Cell Cycling of a Silicon-Majority Anode with a Coulombic Efficiency Exceeding 99.9%. *Energy Environ. Sci.* **2017**, *10* (2), 580–592.
(17) Vericella, J. J.; Baker, S. E.; Stolaroff, J. K.; Duoss, E. B.; Hardin, J. O.; Lewicki, J.; Glogowski, E.; Floyd, W. C.; Valdez, C. A.; Smith, W. L.; Satcher, J. H.; Bourcier, W. L.; Spadaccini, C. M.; Lewis, J. A.; Aines, R. D. Encapsulated Liquid Sorbents for Carbon Dioxide Capture. *Nat. Commun.* **2015**, *6* (1), 6124.
(18) Einloft, S.; Bernard, F. L. Chapter 6 - Encapsulated Liquid Sorbents for CO2 Capture. In *Advances in Carbon Capture*; Rahimpour, M. R., Farsi, M., Makarem, M. A., Eds.; Woodhead Publishing, 2020; pp 125–150.
(19) Hofmeister, I.; Landfester, K.; Taden, A. PH-Sensitive Nanocapsules with Barrier Properties: Fragrance Encapsulation and Controlled Release. *Macromolecules* **2014**, *47* (16), 5768–5773.
(20) Abbaspourrad, A.; Carroll, N. J.; Kim, S.-H.; Weitz, D. A. Polymer Microcapsules with Programmable Active Release. *J. Am. Chem. Soc.* **2013**, *135* (20), 7744–7750.
(21) Zhang, K.; Wu, W.; Guo, K.; Chen, J.; Zhang, P. Synthesis of Temperature-Responsive Poly( *N* -Isopropyl Acrylamide)/Poly(Methyl Methacrylate)/Silica Hybrid Capsules from Inverse Pickering Emulsion Polymerization and Their Application in Controlled Drug Release. *Langmuir* **2010**, *26* (11), 7971–7980.
(22) Amstad, E.; Kim, S.-H.; Weitz, D. A. Photo- and Thermoresponsive Polymersomes for Triggered Release. *Angew. Chem. Int. Ed.* **2012**, *51* (50), 12499–12503.
(23) Wang, X.; Huang, T.; Law, W.-C.; Cheng, C.-H.; Tang, C.-Y.; Chen, L.; Gong, X.; Liu, Z.; Long, S. Controlled Encapsulation and Release of Substances Based on Temperature and Photoresponsive Nanocapsules. *J. Phys. Chem. C* **2018**, *122* (5), 3039–3046.
(24) Radt, B.; Smith, T. A.; Caruso, F. Optically Addressable Nanostructured Capsules. *Adv. Mater.* **2004**, *16* (23–24), 2184–2189.
(25) Liu, T.-Y.; Liu, K.-H.; Liu, D.-M.; Chen, S.-Y.; Chen, I.-W. Temperature-Sensitive Nanocapsules for Controlled Drug Release Caused by Magnetically Triggered Structural Disruption. *Adv. Funct. Mater.* **2009**, *19* (4), 616–623.
(26) Chang, K. S.; Olbricht, W. L. Experimental Studies of the Deformation and Breakup of a Synthetic Capsule in Steady and Unsteady Simple Shear Flow. *J. Fluid Mech.* **1993**, *250*, 609–633.
(27) Stark, K.; Hitchcock, J. P.; Fiaz, A.; White, A. L.; Baxter, E. A.; Biggs, S.; McLaughlan, J. R.; Freear, S.; Cayre, O. J. Encapsulation of Emulsion Droplets with Metal Shells for Subsequent Remote, Triggered Release. *ACS Appl. Mater. Interfaces* **2019**, *11* (13), 12272–12282.
(28) Uebel, F.; Thérien-Aubin, H.; Landfester, K. Tailoring the Mechanoresponsive Release from Silica Nanocapsules. *Nanoscale* **2021**, *13* (36), 15415–15421.
(29) Von Karman, Th.; Tsien, H.-S. The Buckling of Spherical Shells by External Pressure. *J. Aeronaut. Sci.* **1939**, *7* (2), 43–50.
(30) Hutchinson, J. W. Buckling of Spherical Shells Revisited. *Proc. R. Soc. Math. Phys. Eng. Sci.* **2016**, *472* (2195), 20160577.
(31) Vliegenthart, G. A.; Gompper, G. Compression, Crumpling and Collapse of Spherical Shells and Capsules. *New J. Phys.* **2011**, *13* (4), 045020.

(32) Knoche, S.; Kierfeld, J. Buckling of Spherical Capsules. *Phys. Rev. E* **2011**, *84* (4).
(33) Lei, C.; Li, Q.; Yang, L.; Deng, F.; Li, J.; Ye, Z.; Wang, Y.; Zhang, Z. Controlled Reversible Buckling of Polydopamine Spherical Microcapsules: Revealing the Hidden Rich Phenomena of Post-Buckling of Spherical Polymeric Shells. *Soft Matter* **2019**, *15* (32), 6504–6517.
(34) Datta, S. S.; Kim, S.-H.; Paulose, J.; Abbaspourrad, A.; Nelson, D. R.; Weitz, D. A. Delayed Buckling and Guided Folding of Inhomogeneous Capsules. *Phys. Rev. Lett.* **2012**, *109* (13).
(35) Paulose, J.; Nelson, D. R. Buckling Pathways in Spherical Shells with Soft Spots. *Soft Matter* **2013**, *9* (34), 8227–8245.
(36) Munglani, G.; Wittel, F. K.; Vetter, R.; Bianchi, F.; Herrmann, H. J. Collapse of Orthotropic Spherical Shells. *Phys. Rev. Lett.* **2019**, *123* (5), 058002.
(37) Kusters, R.; Simon, C.; Santos, R. L. D.; Caorsi, V.; Wu, S.; Joanny, J.-F.; Sens, P.; Sykes, C. Actin Shells Control Buckling and Wrinkling of Biomembranes. *Soft Matter* **2019**, *15* (47), 9647–9653..
(38) Zoldesi, C. I.; Ivanovska, I. L.; Quilliet, C.; Wuite, G. J. L.; Imhof, A. Elastic Properties of Hollow Colloidal Particles. *Phys. Rev. E* **2008**, *78* (5), 051401.
(39) Pauchard, L.; Couder, Y. Invagination during the Collapse of an Inhomogeneous Spheroidal Shell. *EPL Europhys. Lett.* **2004**, *66* (5), 667.
(40) Berke, L.; Carlson, R. L. Experimental Studies of the Postbuckling Behavior of Complete Spherical Shells. *Exp. Mech.* **1968**, *8* (12), 548–553.
(41) Yang, W.; Yang, J.; Dong, Y.; Mao, S.; Gao, Z.; Yue, Z.; Dillon, S. J.; Xu, H.; Xu, B. Probing Buckling and Post-Buckling Deformation of Hollow Amorphous Carbon Nanospheres: In-Situ Experiment and Theoretical Analysis. *Carbon* **2018**, *137*, 411–418.
(42) Asaka, K.; Miyazawa, K.; Kizuka, T. The Toughness of Multi-Wall Carbon Nanocapsules. *Nanotechnology* **2009**, *20* (38), 385705.
(43) V. Edmond, K.; P. Jacobson, T. W.; Suk Oh, J.; Yi, G.-R.; D. Hollingsworth, A.; Sacanna, S.; J. Pine, D. Large-Scale Synthesis of Colloidal Bowl-Shaped Particles. *Soft Matter* **2021**, *17* (25), 6176–6181.
(44) Li, H.; Zhang, W.; Tong, W.; Gao, C. Enhanced Cellular Uptake of Bowl-like Microcapsules. *ACS Appl. Mater. Interfaces* **2016**, *8* (18), 11210–11214. https://doi.org/10.1021/acsami.6b02965.
(45) Sacanna, S.; Irvine, W. T. M.; Chaikin, P. M.; Pine, D. J. Lock and Key Colloids. *Nature* **2010**, *464* (7288), 575–578.
(46) Mihut, A. M.; Stenqvist, B.; Lund, M.; Schurtenberger, P.; Crassous, J. J. Assembling Oppositely Charged Lock and Key Responsive Colloids: A Mesoscale Analog of Adaptive Chemistry. *Sci. Adv.* **2017**, *3* (9), e1700321.
(47) Zoldesi, C. I.; van Walree, C. A.; Imhof, A. Deformable Hollow Hybrid Silica/Siloxane Colloids by Emulsion Templating. *Langmuir* **2006**, *22* (9), 4343–4352.
(48) Meeuwissen, S. A.; Kim, K. T.; Chen, Y.; Pochan, D. J.; van Hest, J. C. M. Controlled Shape Transformation of Polymersome Stomatocytes. *Angew. Chem.* **2011**, *123* (31), 7208–7211.
(49) Ross, F. M. Opportunities and Challenges in Liquid Cell Electron Microscopy. *Science* **2015**, *350* (6267), aaa9886–aaa9886.
(50) Liao, H.-G.; Zheng, H. Liquid Cell Transmission Electron Microscopy. *Annu. Rev. Phys. Chem.* **2016**, *67* (1), 719–747.

(51) B. Alam, S.; Yang, J.; C. Bustillo, K.; Ophus, C.; Ercius, P.; Zheng, H.; M. Chan, E. Hybrid Nanocapsules for in Situ TEM Imaging of Gas Evolution Reactions in Confined Liquids. *Nanoscale* **2020**, *12* (36), 18606–18615.
(52) Ianiro, A.; Wu, H.; Rijt, M. M. J. van; Vena, M. P.; Keizer, A. D. A.; Esteves, A. C. C.; Tuinier, R.; Friedrich, H.; Sommerdijk, N. A. J. M.; Patterson, J. P. Liquid–Liquid Phase Separation during Amphiphilic Self-Assembly. *Nat. Chem.* **2019**, *11*, 320.
(53) Hoppe, S. M.; Sasaki, D. Y.; Kinghorn, A. N.; Hattar, K. In-Situ Transmission Electron Microscopy of Liposomes in an Aqueous Environment. *Langmuir* **2013**, *29* (32), 9958–9961.
(54) Touve, M. A.; Figg, C. A.; Wright, D. B.; Park, C.; Cantlon, J.; Sumerlin, B. S.; Gianneschi, N. C. Polymerization-Induced Self-Assembly of Micelles Observed by Liquid Cell Transmission Electron Microscopy. *ACS Cent. Sci.* **2018**, *4* (5), 543–547.
(55) Patterson, J. P.; Wu, H.; Ianiro, A.; Su, H.; Esteves, A. C. C.; Tuinier, R.; Friedrich, H.; Sommerdijk, N. A. J. M. Liquid Phase Electron Microscopy of Soft Matter. *Microsc. Microanal.* **2018**, *24* (S1), 248–249.
(56) Parent, L. R.; Bakalis, E.; Ramírez-Hernández, A.; Kammeyer, J. K.; Park, C.; de Pablo, J.; Zerbetto, F.; Patterson, J. P.; Gianneschi, N. C. Directly Observing Micelle Fusion and Growth in Solution by Liquid-Cell Transmission Electron Microscopy. *J. Am. Chem. Soc.* **2017**, *139* (47), 17140–17151.
(57) Kim, M. D.; Dergunov, S. A.; Richter, A. G.; Durbin, J.; Shmakov, S. N.; Jia, Y.; Kenbeilova, S.; Orazbekuly, Y.; Kengpeiil, A.; Lindner, E.; Pingali, S. V.; Urban, V. S.; Weigand, S.; Pinkhassik, E. Facile Directed Assembly of Hollow Polymer Nanocapsules within Spontaneously Formed Catanionic Surfactant Vesicles. *Langmuir* **2014**, *30* (24), 7061–7069.
(58) Kim, M. D.; Dergunov, S. A.; Pinkhassik, E. Controlling the Encapsulation of Charged Molecules in Vesicle-Templated Nanocontainers through Electrostatic Interactions with the Bilayer Scaffold. *Langmuir* **2017**, *33* (31), 7732–7740.
(59) Yuk, J. M.; Park, J.; Ercius, P.; Kim, K.; Hellebusch, D. J.; Crommie, M. F.; Lee, J. Y.; Zettl, A.; Alivisatos, A. P. High-Resolution EM of Colloidal Nanocrystal Growth Using Graphene Liquid Cells. *Science* **2012**, *336* (6077), 61–64.
(60) Yang, J.; Alam, S. B.; Yu, L.; Chan, E.; Zheng, H. Dynamic Behavior of Nanoscale Liquids in Graphene Liquid Cells Revealed by in Situ Transmission Electron Microscopy. *Micron* **2019**, *116*, 22–29.
(61) Dergunov, S. A.; Khabiyev, A. T.; Shmakov, S. N.; Kim, M. D.; Ehterami, N.; Weiss, M. C.; Birman, V. B.; Pinkhassik, E. Encapsulation of Homogeneous Catalysts in Porous Polymer Nanocapsules Produces Fast-Acting Selective Nanoreactors. *ACS Nano* **2016**, *10* (12), 11397–11406.
(62) Knoche, S.; Kierfeld, J. The Secondary Buckling Transition: Wrinkling of Buckled Spherical Shells. *Eur. Phys. J. E* **2014**, *37* (7), 62.
(63) Quilliet, C. Numerical Deflation of Beach Balls with Various Poisson's Ratios: From Sphere to Bowl's Shape. *Eur. Phys. J. E* **2012**, *35* (6), 48.
(64) Nielsen, M. H.; Aloni, S.; Yoreo, J. J. D. In Situ TEM Imaging of CaCO3 Nucleation Reveals Coexistence of Direct and Indirect Pathways. *Science* **2014**, *345* (6201), 1158–1162.

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