Salt-Induced Swelling-to-Shrinking Transition in Polyelectrolyte Multilayer Capsules

Karen Köhler, P. Maarten Biesheuvel,* Richard Weinkamer, Helmuth Möhwald, and Gleb B. Sukhorukov

Max Planck Institute of Colloids and Interfaces, Wissenschaftspark Golm, 14424 Potsdam, Germany

(Received 29 June 2006; published 31 October 2006)

We study the size of polyelectrolyte multilayer capsules as a function of ionic strength, temperature, and time. A dynamic micromechanical model is developed which successfully describes the experiments. The model includes the polymer-solvent surface tension, an electrostatic force which is strongly ionic strength dependent, and a temperature-dependent mobility parameter. The activation of >50 kT suggests that multiple ion pairs must be broken simultaneously in the process of chain rearrangement. In support of our physical model capsules can repeatedly swell and shrink by varying ionic strength.

DOI: 10.1103/PhysRevLett.97.188301 PACS numbers: 82.35.Rs, 05.70.Ln, 41.20.Cv, 82.70.Dd

Hollow polyelectrolyte multilayer microcapsules can be prepared by alternately coating charged template particles with polycations and polyanions, after which the template particles are dissolved [1]. Ionic bonds, or "ion pairs", between polycation and polyanion segments give the shell wall (of a thickness on the order of ~20 nm) mechanical stability, while under the influence of external forces such as temperature, *p*H, and added salt these capsules shrink (ultimately to a full sphere), or swell, even to the point of exploding. Because of the sensitive dependence of size and wall thickness (thus permeability) on environmental stimuli, these capsules have technological potential in biomedical and nanotechnological applications as chemical microcontainers, controlled-release microtransporters for drugs, etc. Furthermore, they are an interesting (biomimetic) model system to study dynamic processes and equilibrium for (charged) capsules and vesicles in aqueous media in general. In contrast, lipid-based vesicles (liposomes) have a constant wall thickness and can therefore only change in size by recombining with other vesicles or by budding off smaller ones. Consequently, it is not straightforward to obtain thermodynamic equilibrium structures, let alone to study a (gradual) size change as a function of external parameters [2]. Finally, multilayer structures can be considered a novel class of reversibly crosslinked polymeric materials, in the form of ultrathin films [3]. They are thus well-defined model systems to study the interplay of short-range attractive (mostly hydrophobic) and long-range (electrostatic and entropic) interactions.

For most combinations of polycations and polyanions the polyelectrolyte multilayer capsules shrink when heated (at room temperature most capsule systems are effectively "frozen in"). This is probably due to a positive surface tension (because the polyelectrolytes comprising the capsule are hydrophobic) which results in a contractive force. It was recently shown that in pure water capsules made from the combination of the polyanion polystyrenesulfonate (PSS, $M_W = 70$ kDa) and the polycation polydiallyldimethylammoniumchloride (PDADMAC, 350 kDa), with PDADMAC forming the last layer, actually swell—and quite significantly so—whereas PSS-terminated multilayers shrink [4], which can be explained by assuming that for the PDADMAC-finalized structures the net excess charge is higher, making the electrostatic expansive force higher, or that the PSS-terminated capsules are more hydrophobic. The significant difference in swelling behavior between these two chemically so similar systems shows that hydrophobic and electrostatic forces are in a subtle balance. This is made more evident in the present work where we will show that even within the class of the PDADMAC-terminated capsules we can subtly change the balance of these forces by external means, especially ionic strength, making this system reversibly and repeatedly switch from swelling to shrinking and back.

To calculate the electrostatic force, we describe the capsule shell wall as an infinitely thin charged plane with the counterions not within the polymer structure, but as a diffuse ion cloud on each side of the plane. For more details of this approach, with supporting references both to theoretical and experimental work, see [5]. In the Debye-Hückel (DH) low-potential limit, the electrostatic free energy (in kT) per capsule is given by $E^{\mathrm{elec}} = \frac{1}{2}Zy$ where Z is the net polymer charge per capsule (number of elementary charges) and y the dimensionless capsule electrostatic potential. Using the DH assumption for the *two* ion clouds next to the charged plane we obtain

$$y = \frac{2\lambda_B}{\kappa}\frac{Z}{D^2}, \tag{1}$$

where κ^{-1} is the Debye length, λ_B the Bjerrum length related to κ according to $\kappa^2 = 8\pi\lambda_B n_\infty$, (we use $\lambda_B = 0.72$ nm at all temperatures because the product ϵT in the definition of $\lambda_B = e^2/4\pi\epsilon kT$ is almost T independent), n_∞ the ionic strength (in numbers per volume unit, obtained by multiplying the ionic strength c_∞, expressed in mM, by N_{av}), and D the capsule diameter. The electrostatic force is obtained by taking the negative derivative of E^{elec} with size D, which results in

$$f^{\text{elec}} = \frac{Zy}{D} = 2\frac{Z^2\lambda_B}{D^3\kappa}, \tag{2}$$

which is always positive (expansive).

Opposing the electrostatic force is a contractive force due to the hydrophobicity of the polymer chains, which tends to minimize the contact area of the shell with the solvent. The hydrophobic contribution to the surface energy is given by $E^{\text{surf}} = 2\pi D^2\sigma$, where σ is the surface tension. The surface force then follows as

$$f^{\text{surf}} = -4\pi\sigma D, \tag{3}$$

which for $\sigma > 0$ is always negative (contractive).

When the summation of these two forces is equal to zero, an equilibrium size will be reached, which can be below or above the initial size, D_0, dependent on ionic strength, surface charge, and surface tension. The equilibrium size follows from the combination of Eqs. (2) and (3) and is given by

$$D_\infty = \sqrt[4]{\frac{Z^2\lambda_B}{2\pi\kappa\sigma}}. \tag{4}$$

To describe the rate of change of the capsule size from its initial to its final value, we ideally would have to incorporate the molecular forces resisting the change in capsule size into a dynamic model. These forces are probably due to slow chain rearrangements within the shell, related to the destruction and reformation of PSS-PDADMAC ion pairs. However, because the dynamic details of these processes are not well known, we have decided to follow a more phenomenological route. A first option seems to be to describe the shell wall as a viscous liquid. However, solving the Navier-Stokes equation for a Newtonian liquid results in the fact that for isotropic expansion viscosity is irrelevant because fluid "packets" do not flow along each other but are only deformed (in expansion compressed in radial and expanded in longitudinal direction). Therefore, we decided to describe the rate of size change as the product of the net force acting on the shell and a capsule "mobility", μ,

$$\frac{dD}{dt} = \mu(f^{\text{surf}} + f^{\text{elec}}), \tag{5}$$

where t is time. Inserting Eqs. (2) and (3) in Eq. (5) gives a differential equation, which after integration results in $D = \sqrt[4]{D_\infty^4 - (D_\infty^4 - D_0^4)\exp(-16\pi\sigma\mu t)}$, where the final diameter, D_∞, is given by Eq. (4).

Comparison of Eq. (4) with the data showed that the charge Z is not simply a constant but is a function of the (local, i.e., near the shell) ion concentration. To describe this effect we assume that all polyanion segments are charge compensated by the (excess) polycation segments (e.g., in the form of ion pairs), whereas to the excess polycation segments anions can adsorb. We describe this reaction by a classical Langmuir isotherm for which the charge Z is given by

$$Z = \frac{Z_0}{1 + K_S n_\infty e^y}, \tag{6}$$

where Z_0 is the capsule charge in the absence of absorbing ions and K_S is an equilibrium constant describing the strength of ion adsorption. During capsule expansion both y and Z change and therefore Eq. (5) cannot be directly integrated analytically, but must be solved numerically in combination with Eqs. (1)–(3) and (6).

We first compare the dynamic model with data for the final, equilibrium, size. A first consideration is to find a proper value for the surface tension σ. Combining Eqs. (1) and (4) we find the interesting result that the equilibrium electrostatic potential of the capsule, y_∞, relates to σ according to $y_\infty = \sqrt{8\pi\lambda_B\sigma\kappa^{-1}}$, irrespective of capsule size or charge. Now, with y values (e.g., estimated using zeta-potential measurements) typically in the order of 10–50 mV for self-assembled polyelectrolyte systems [4], we can derive that σ^* (divide the dimensional σ^* by kT to obtain σ to be used in the theory) should be around 100 μN/m, a quite realistic value for the interface between water and (phase-separated) hydrated charged polymer mixtures [6] (surface tensions of water-oil or water-air interfaces are typically up to the order of ~1000 times higher). With this value we have a surface potential ranging from ~20 mV at 50 mM to ~60 mV at $c_\infty = 0.5$ mM. A 10 times increased value for σ would give values for y_∞ of 60 and 190 mV, which are unrealistically high.

Experimental data for the 9-layer PDADMAC-terminated capsules (wall thickness ~20 nm when $D = D_0 = 4.5$ μm) are presented in Fig. 1(b) (see [4] for details on synthesis and data analysis). With the addition of salt the equilibrium size is reduced, and for c_∞ beyond ~10 mM the capsules, starting from their initial size of ~4.5 μm, no longer swell but instead now shrink. We see a small effect of temperature on the equilibrium size which

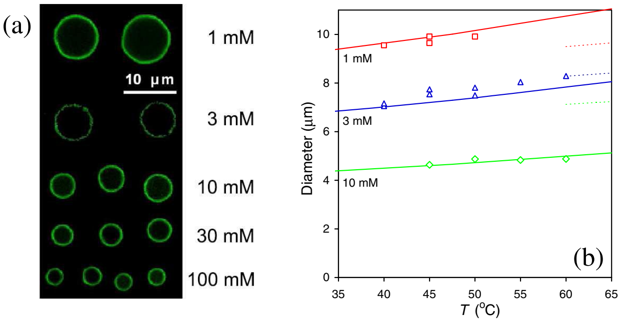

FIG. 1 (color online). PSS-PDADMAC multilayer capsules. (a) Confocal images using fluorescence markers as a function of ionic strength c_∞ ($t = 20$ min, temperature $T = 45°$C). (b) Equilibrium diameter as a function of T and c_∞. Solid lines according to theory based on a Langmuir isotherm; dashed lines assuming a fixed charge.

we assume to be due to a small decrease of the surface tension with temperature. From Fig. 1(b) we extract an empirical temperature dependence of σ^* (namely $\sigma^* = 140 - T$ with T in °C and σ^* in μN/m), as well as (T-independent values) for the Langmuir parameters Z_0 and K_S. These were obtained from rewriting Eqs. (4) and (6) with the expression for y_∞ to $\frac{1}{D_\infty^2 y_\infty}\sqrt{\frac{\lambda_B}{2\pi\sigma\kappa}} = \frac{1}{Z_0} + \frac{K_S}{Z_0} n_\infty e^{y_\infty}$. Based on the data for D_∞ vs n_∞ we can plot the left-hand side as a function of $n_\infty e^{y_\infty}$, and calculate Z_0 and K_S from slope and abscissa. A linear fit is obtained from which we derive values of $Z_0 = 2.85 \times 10^7$ and $K_S = 230$ nm^3. The result of using these parameters is plotted as theoretical curves in Fig. 1(b). If Z would be constant, not influenced by ion adsorption, and thus independent of ionic strength ($K_S = 0$) a proper fit is impossible, see the set of dashed lines in Fig. 1(b) based on $Z = Z_0 = 1.2 \times 10^7$ ($K_S = 0$). Clearly, the influence of salt is not just a screening effect (reduction of electrostatic potential) but also due to ion adsorption, thereby reducing the surface charge.

Experimental data for the diameter after 20 min of swelling at different temperatures and ionic strength are presented in Fig. 2(a). We observe the same dependence of diameter on c_∞ as in Fig. 1, while the influence of T is larger because (below 50°C) we are not yet at equilibrium, and we have a T-dependent rate constant, which we describe as an activated process, i.e., according to $\mu = \mu_0 \exp[-\frac{E_A}{k}(\frac{1}{T} - \frac{1}{T_0})]$ ($T_0 = 298$ K). This procedure works rather well, though it is difficult to derive an exact value for the activation energy. We have decided to use $\frac{E_A}{k} = 16.7 \times 10^3$ K, thus $E_A = 56$ kT ($\mu_0 = 0.225$ nm^2/h); see the solid lines in Fig. 2(a). Using values for E_A that are 20 kT higher/lower we obtain the dashed lines in Fig. 2(a). Certainly the lower value (36 kT, more shallow dashed line) can be considered to be too low; however, the value of 76 kT (steeper dashed line) would also describe the data rather well. In any case, the high values for kT suggest that many bonds have to be broken at the same time for chain rearrangement to occur; if just a single ion pair had to be broken, an activation energy of a few kT could be expected.

Figure 2(b) shows similar data, all at 40°C, in a wider range of ionic strength ($t = 20$ min; to calculate κ we include an additional very small concentration of $c_\infty = 30$ μM salt, e.g., remaining in the original capsule suspension after preparation). As in Fig. 2(a) we see that (beyond 0.1 mM) the capsule size decreases with increasing c_∞. Interestingly, a maximum in size is observed around $c_\infty = 0.1$ mM with the size decreasing again at even lower c_∞. When we assume a fixed charge $Z = Z_0$ we are unable to describe the data at all, neither the gradual decrease for moderately high c_∞ (> 0.3 mM), nor the maximum around 0.1 mM (see dashed line). Instead, the model incorporating the Langmuir isotherm for anion adsorption describes the data quite well, with the change of size with ionic strength beyond 0.3 mM reasonably well described, but more interestingly, also predicting the maximum in size around 0.1 mM.

What is the origin of the maximum? First of all, for a shell of a fixed charge the electrostatic expansive force will always decrease with higher c_∞ due to a screening effect [lower y, see dashed line in Fig. 2(b)]. Instead, when the surface charge, Z, depends on c_∞, e.g., according to Eq. (6), with increasing c_∞, y is reduced but simultaneously Z increases; at low c_∞ the product increases with c_∞ resulting in a further expansion with increasing c_∞. This phenomenon is closely related to the osmotic regime found at low c_∞ for ionizable polyelectrolyte brushes—see discussion and references given in [5]—as well as to a nonmonotonic ion-strength dependence of phase transitions in phospholipid membranes [7].

Time-dependent experiments are presented in Fig. 3(a). Fitting the theory to the data, the full curves are obtained.

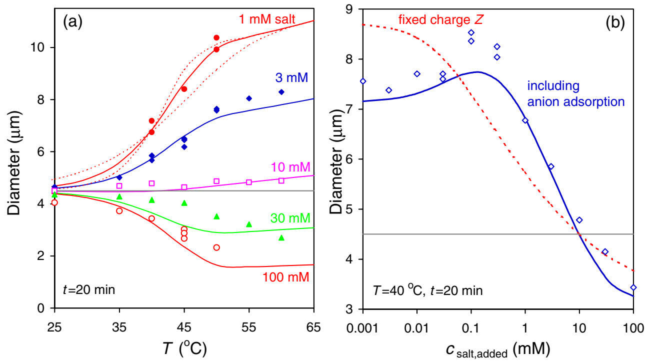

FIG. 2 (color online). Capsule size as a function of T and c_∞. All lines based on $E_A = 56$ kT, except for dashed lines in (a) for which $E_A = 36$ or 76 kT; (b) dashed line based on $Z = Z_0 = 5.36 \times 10^6$.

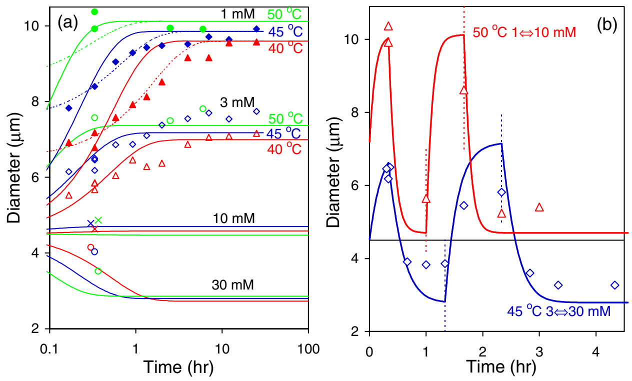

FIG. 3 (color online). Size of capsules as a function of temperature, time, and ionic strength. Lines from theory discussed in the text. In (b) ionic strength is repeatedly switched between 1(3) and 10(30) mM.

For the data sets at 3 mM a good fit to the data is obtained using the exact same parameter settings as before. However, for the data at 1 mM the situation is less satisfactory, with the experiments on the one hand showing a very rapid size increase even before the first data point (10 min), with thereafter a rate for size change that is much slower than for the previous data at higher ionic strength. The dashed lines include these two effects, first of all by assuming empirically an initial size given by $D_0(\mu\text{m}) = 0.2T(^\circ\text{C})–1.5$ and, second, by reducing μ_0 by a factor of 3, to $\mu_0 = 0.075\ \text{nm}^2/\text{h}$. Experiments without added salt (not reported here) can be described using the same parameter settings.

Though we certainly do not have clear answers to understand the qualitative difference of the data at ≤ 1 mM compared to those at ≥ 3 mM, it can be remarked that the rapid initial size change may be due to a swelling of the shell wall itself (chains moving further apart), which will directly result in a size increase. That this only occurs at or below 1 mM, and not above, might be due to the very low screening of the polymer charges within the shell at low c_∞. At higher ionic strength screening within the capsule is more effective, chains are more closely packed, and upon heating do not move further apart. The lower mobility at low c_∞ points to the role of small ions as catalyst for the breakup and reformation of ion pairs [3]. A higher c_∞ facilitates the destruction of polycation-polyanion ion pairs (possibly also because up to a few mM the number of "free" polycation ion segments—without a condensed counterion—increases with c_∞), making chain rearrangement easier, leading to a higher mobility, μ.

Until now we have only considered capsule histories in which the size is either continuously increasing or decreasing in time. Though the theory implicitly predicts that a swollen capsule will shrink again when brought in a solution of higher ionic strength, this reversibility, or switching behavior, has not yet been experimentally established. Therefore, we performed the following experiments at 45–50°C: (i) we bring capsules in contact with 1 mM (3 mM) salt solution; (ii) after 20 min we add salt such that the ionic strength increases tenfold, and wait for 40 (60) min; (iii) we dilute tenfold with distilled water, wait again; and (iv) again add salt to increase the ionic strength tenfold.

Theoretically, see the curves in Fig. 3(b), we expect a reversible switching between a large capsule diameter at the low-c_∞ condition, and a much smaller one at higher c_∞, while for the $3 \leftrightarrow 30$ mM experiment we expect the capsules to go repeatedly from above to below the initial diameter ($D_0 = 4.5\ \mu\text{m}$). This prediction is borne out by the experiment, with indeed a repeated cycling between a larger and smaller capsule size observed.

In conclusion, we studied the influence of ionic strength and temperature on the microdynamics of multilayer capsules. We show that their size is determined by a fine balance between an electrostatic and a hydrophobic component of the surface force, a balance that can be accurately controlled and quantified. An activation energy of $\gtrsim 50$ kT is estimated, pointing to the involvement of multiple ion pairs in the process of chain rearrangement. We report repeated swelling and shrinking, in which we changed the capsule volume reversibly by a factor of ~5, after changing the ionic strength tenfold, at time scales of less than 1 h at still moderate temperatures of only ~45–50°C. To our knowledge such reversible swelling-shrinking as a function of ionic strength has not been reported before for any kind of vesicle or capsule. This phenomenon might be relevant for the use of these polyelectrolyte multilayer structures as microcontainers, microreactors, micropumps, and/or microtransporters, e.g., in biomedical applications: when brought in a higher ionic strength environment the capsules shrink and release ~80% of their cargo; back in a low-salt environment they will take up 4 times their volume with "fresh" solution. As a final comment, both experiments and the model show that salt and temperature do *not* affect the polyelectrolyte films in a similar fashion, as argued in [8].

This research was financially supported by the European Union and the Alexander von Humboldt Foundation.

---

[*] Electronic address: maarten.biesheuvel@mpikg.mpg.de

[1] E. Donath, G. B. Sukhorukov, F. Caruso, S. A. Davis, and H. Möhwald, Angew. Chem., Int. Ed. **37**, 2201 (1998); C. S. Peyratout and L. Dähne, Angew. Chem., Int. Ed. **43**, 3762 (2004); J. Heuvingh, M. Zappa, and A. Fery, Langmuir **21**, 3165 (2005).
[2] M. M. A. E. Claessens, B. F. van Oort, F. A. M. Leermakers, F. A. Hoekstra, and M. A. Cohen Stuart, Biophys. J. **87**, 3882 (2004).
[3] J. A. Jaber and J. B. Schlenoff, J. Am. Chem. Soc. **128**, 2940 (2006).
[4] C. Gao, S. Leporatti, S. Moya, E. Donath, and H. Möhwald, Chem. Eur. J. **9**, 915 (2003); K. Köhler, D. G. Shchukin, H. Möhwald, and G. B. Sukhorukov, J. Phys. Chem. B **109**, 18 250 (2005); K. Köhler, H. Möhwald, and G. B. Sukhorukov, J. Phys. Chem. B (to be published).
[5] P. M. Biesheuvel, T. Mauser, H. Möhwald, and G. B Sukhorukov, Macromolecules (to be published).
[6] E. Scholten, R. Tuinier, R. H. Tromp, and H. N. W. Lekkerkerker, Langmuir **18**, 2234 (2002).
[7] C. A. Helm, L. Laxhuber, M. Lösche, and H. Möhwald, Colloid Polym. Sci. **264**, 46 (1986).
[8] H. L. Tan, M. J. McMurdo, G. Pan, and P. G. van Patten, Langmuir **19**, 9311 (2003).