Drug Release

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# Strain-Controlled Release of Molecules from Arrayed Microcapsules Supported on an Elastomer Substrate**

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Over the last two decades, considerable attention has been paid to the controlled release of drugs. Most studies have focused on sustained release from a variety of drug-containing carriers.[1–4] However, there are many clinical situations that require more than a prolonged, continuous release of drugs.[5] For example, chronopharmacological studies indicate clear temporal or physical dependence of the onset of certain diseases on circadian rhythms.[6] The treatment of such diseases would benefit from smart control over the release pattern of a drug in response to in vivo physiological changes or external stimulations.[7–9] A fast response of the drug carrier to the stimuli may enable real-time control of the dosage. The concept of stimuli-regulated release has been studied for changes in the pH value[10] or temperature,[11,12] ultrasound,[5,6] and electric[13,14] or magnetic fields,[15,16] but has not been applied to mechanical strain, although this stimulus is ubiquitous in the body or very simple to apply externally. Strain changes are involved in many processes, such as compression in cartilage and bones, tension in muscles and tendons, and shear force in blood vessels. Strain-controlled release, if possible, could be applied in patches that respond to body motions, without the need for continuous release in vain. It would also be useful for implanted patches that could synchronize with the mechanical motions of organs, muscles, and tendons.

This study suggests a concept for the realization of strain-controlled release. We demonstrate the fabrication of arrayed microcapsules supported on an elastomer substrate. The arrayed microcapsules were obtained by using buckled polymer thin films, which can provide stretchability without defects.[17] The stretchable microcapsules were prepared according to the schematic illustration in Figure 1a (for more detail, see the Supporting Information). Heating and cooling of a solid polymer thin film on a rubbery substrate, a polystyrene (PS) layer on a poly(dimethylsiloxane) (PDMS) substrate in this study, leads to isotropic buckling (see Figure S1 in the Supporting Information). The placement of a line-and-space PDMS mold on top of the PS layer, followed by thermal heating and cooling, produced a buckled pattern in the PS layer, as defined by the trenches of the PDMS mold.[18,19] When both the PS layer and the PDMS mold were treated with $O_2$ plasma before contact, the PS layer in contact with the PDMS mold was peeled off with the mold when the mold was removed, and PS stripes with buckled features were left behind on the substrate. When the buckled substrate was

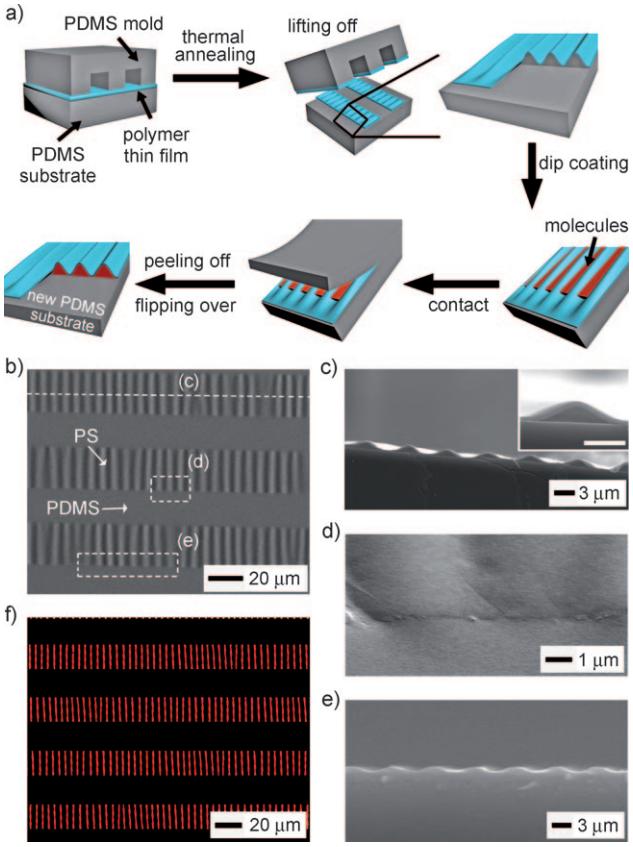


***Figure 1.*** a) Schematic illustration of the buckling and transfer process for the preparation of arrayed microcapsules. b–e) SEM images of the fabricated microcapsules: b) top view and c) cross-sectional view of the microcapsules; d) tilted view and e) side view of the edge of the buckled structures. The inset in (c) shows a further-magnified image of a capsule (scale bar: 2 μm). f) Optical microscope image showing fluorescence from rhodamine B loaded in the microcapsules.

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dipped in an aqueous solution containing target molecules, the molecules were selectively loaded in the troughs of the buckled structure. After drying, the buckled stripes were transferred onto another flat PDMS substrate by simple physical contact. Since PS is glassy at room temperature ($T_g$ ca. 100 °C), the transferred PS layer maintained an array of chambers loaded with the target molecules. During the transfer process, both ends of each chamber were attached to the new PDMS surface to produce an array of microcapsules with sealed ends.

Figure 1 b shows an SEM image of the buckled structure after transfer to the new PDMS substrate. Since the adhesion between the PS layer and the new PDMS surface had to be stronger than that between the PS layer and the initial PDMS surface, a softer PDMS material was employed as the new substrate. The prepolymer/cross-linker ratio was 20:1 (w/w) for the new substrate and 10:1 (w/w) for the initial substrate. The dip-coating process for drug loading also facilitated transfer of the buckled layer, because water infiltration into the interface between the hydrophobic PS surface and the plasma-treated hydrophilic PDMS surface weakens the adhesion.[20,21] Without the dip-coating step, the buckling layer was only partly transferred or destroyed (see Figure S2 in the Supporting Information). A cross-sectional view of the transferred buckling pattern showed that each buckled structure formed a microscale chamber (Figure 1 c; the inset shows a magnified image of the cross-sectional view). A tilted view indicated that the edges of the transferred structures were tightly sealed (Figure 1 d). The cross-sectional view in Figure 1 e further confirmed that both ends of each chamber were closed to form an array of isolated microcapsules. The chambers could serve as reservoirs for molecules. Fluorescence optical microscopy clearly showed organic dyes (rhodamine B) loaded in the microcapsules (Figure 1 f). Water-soluble polymers can also be loaded into the microcapsules by using the same procedure, as demonstrated with FITC-labeled dextran ($M_w = 10\,000$; see Figure S3 in the Supporting Information; FTIC = fluorescein isothiocyanate).

Upon repeated stretching and release, the microcapsules maintained the initial structure without any cracks or peeling (see Figure S4 in the Supporting Information). Figure 2 shows AFM images before and after the application of 6.5 % strain. Cross-sectional analysis of Figure 2 b showed that the capsules at 6.5 % strain were deformed into hat-shaped structures. The curve in Figure 2 c shows the changes in wavelength and amplitude as a function of the strain applied to the PDMS substrate. The height profiles obtained from AFM analysis were used to determine both wavelength and amplitude. The wavelength ($\lambda$) and amplitude ($A$) of buckling under external stretching varies according to the following equations:[22] $\lambda = \lambda_0(1+\varepsilon_{applied})$ and $A = h[(\varepsilon_{pre}-\varepsilon_c-\varepsilon_{applied})/\varepsilon_c]^{0.5}$, in which $\lambda_0$ is the wavelength of nonstretched buckling, $h$ is thickness of the PS layer, $\varepsilon_{pre}$ is the prestrain applied to cause the initial buckling, and $\varepsilon_c$ is the critical strain for buckling. The predictions from these equations (solid lines) were in good agreement with the measured values (filled circles; Figure 2 c). Upon stretching to 7.5 %, the wavelength increased to $5.84 \pm 0.11$ μm, and the amplitude decreased to $18 \pm 12$ nm to give an almost flat structure. The deformed microcapsules

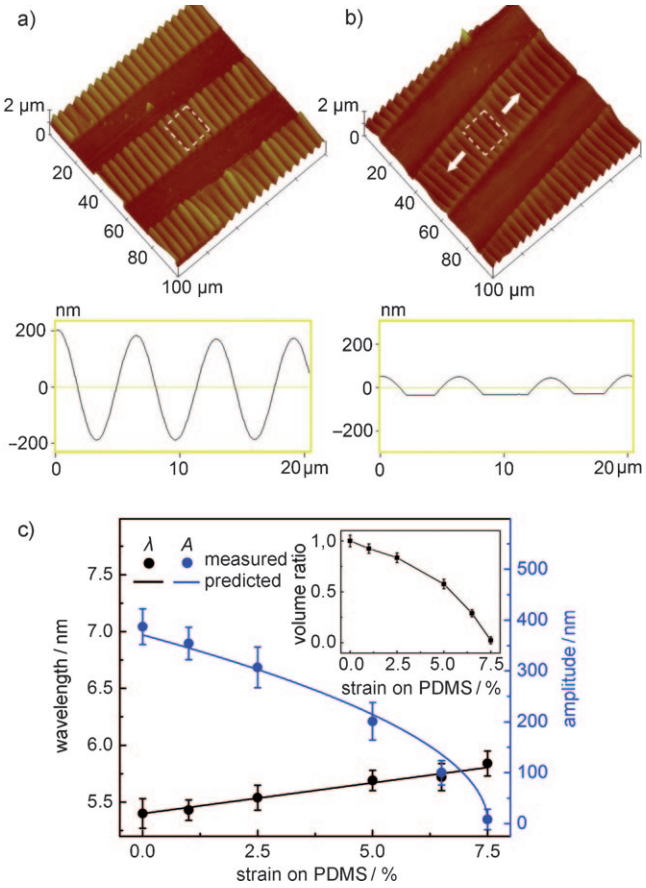


***Figure 2.*** a,b) AFM images showing changes in the dimensions of the microcapsules as a result of mechanical stretching: a) no stretching; b) 6.5 % stretching along the direction indicated by the white arrows. c) Plots showing changes in wavelength and amplitude as a function of strain applied to the PDMS substrate. The inset shows the relative volume change of the microcapsules as a function of the applied strain.

could recover the initial shape and volume when the applied strain was removed. Assuming that the surface profile of the microcapsules is sinusoidal, that is, $W = (A/2)\sin(2\pi x/\lambda)$, the maximum strain is placed on the crests and troughs, where the curvature is the largest. The maximum strain is given by:[17]

$$\varepsilon_{max} \approx \frac{\pi^2 A h}{\lambda^2}$$

At a strain of 7.5 % on the PDMS substrate, the maximum strain at the crests of the microcapsules with a 68 nm thick polymer layer was calculated to be approximately 0.90 %, which is below the fracture limit of bulk PS of 1–4 %.[23] This result indicates that the strain on the microcapsules is much less than the strain applied to the substrate; therefore, the microcapsules have high tolerance toward stretching. When a strain of 8.5 % was applied to the PDMS substrate, the microcapsule structure became flat. Cracks formed in the fully extended polymer film at above 8.5 % strain, and the capsule structure could not be restored (see Figure S5 in the Supporting Information). The inset in Figure 2 c shows the relative volume change of the microcapsules as calculated

from the wavelength and the amplitude. The volume change should be the same as the variation in the cross-sectional area of the microcapsules. For example, a strain of 2.5% on the PDMS substrate reduced the volume of the microampoules by 17%, and a strain of 7.5% led to a 98% decrease in volume.

In the membrane-controlled release system, a reservoir is first filled with the solvent, and the molecules dissolved by the solvent in the reservoir diffuse out with the solvent through the polymer membrane. The surface of the microcapsules was treated with $CF_4$ plasma to create a hydrophobic skin layer. The hydrophobic layer could act as a diffusion barrier for water, and thus retard the release of molecules from the microcapsules. Figure 3a shows the release profiles of rhodamine B and FITC-labeled dextran. Without any stretching, 7% of rhodamine B molecules were gradually released in 45 min. The release exhibited a linear profile over time, as typically observed in a membrane-controlled release system.[24] In comparison, no release was observed for FITC-labeled dextran. This difference can be attributed to the difference in molecular weight of the molecules. The transportation of molecules through a solid polymer matrix can be described by two mechanisms: 1) diffusion through free volumes of the membrane and 2) diffusion assisted by the wriggling of polymer chains.[25] The small rhodamine B molecules can diffuse through the interchain free volumes, whereas large dextran molecules cannot pass through without reptational motion of the membrane chains. Since the motion of PS polymer chains was restricted at room temperature, the dextran molecules could not diffuse out from the microcapsules.

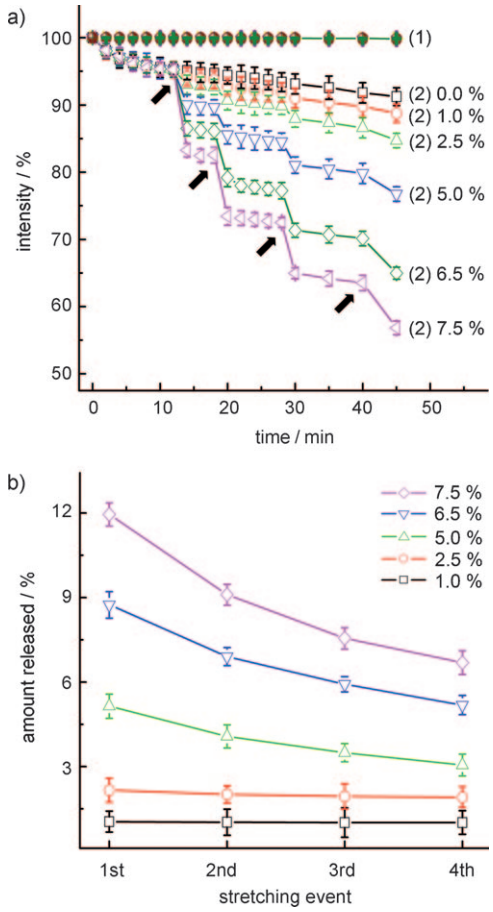


***Figure 3.*** Release behavior of the molecules from the microcapsules: a) Release profiles of 1) FITC-labeled dextran ($M_w = 10000$) and 2) rhodamine B at various strains. Black arrows indicate the points at which mechanical stretching was applied. b) Plots showing the amount of rhodamine B pumped out upon stretching during consecutive stretching and release events. The strain rate was 0.1% $s^{-1}$.

Upon repeated mechanical stretching of the substrate at 1% strain, approximately 1% of the rhodamine B was pumped out at each stretching event. The steplike release behavior was clearly observed at larger strains. When the strain was removed, the release of rhodamine B followed the release profile observed for the microcapsules without any stretching. We found that the amount of rhodamine B released was determined by the degree of strain, but the strain rate could also provide some variation (see Figure S6 in the Supporting Information). At large strain rates, resistance of the liquid medium to the quick movement of the polymer membrane resulted in additional pressure and increased the amount of pumping. When a constant strain was maintained for a long time, the release of rhodamine B soon reached its equilibrium: after prompt release of the initial amount, the profile observed without any strain was followed (see Figure S7 in the Supporting Information). As shown in the inset in Figure 2c, the volume of the microcapsules decreased by 17, 42, 71, and 98% from the initial volume under strains of 2.5, 5, 6.5, and 7.5%, respectively. Figure 3b shows the amount of rhodamine B released upon repeated stretching events. As the number of stretching events increased, the pumping effect was weakened, since the remaining rhodamine B was diluted further each time mechanical stretching was applied. For example, the first stretching event at 2.5% strain released 2.2% rhodamine B, whereas the fourth stretching event led to 1.9% release. This behavior was amplified at larger strains. The FITC–dextran molecules were not released, regardless of the number of stretching events.

Hydrogel-assisted microcapsules were investigated as a practical application of the concept of strain-controlled molecule release (Figure 4). The hydrogel patterns were directly fabricated by UV curing of a mixture film of poly(ethylene glycol) diacrylate (PEGDA) and 2-hydroxy-2-methylpropiophenone cast on the arrayed microcapsules.[26] The inset of Figure 4a is a further-magnified image showing the square hydrogel features and the well-preserved buckled structure. Since the patterned hydrogel was still hydrated under ambient conditions, the strain applied to the substrate could release the molecules selectively from the hydrogel-covered regions. The fluorescence image in Figure 4b confirms the selective release from the gel-patterned areas, whereas no release was observed in other regions. If the structure in Figure 4a was used as a patch, the gel-covered regions should provide fast release for immediate medication, whereas the other regions could be used for prolonged release under strain. Furthermore, the gel-patterned structures could obstruct the direct contact of the microcapsules with the skin layer and thus prevent possible deformation or fracture of the microcapsules. Figure 4c,d show how the hydrogel-assisted

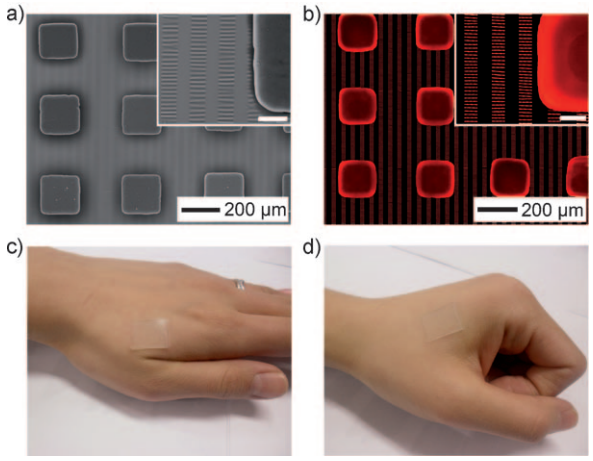


***Figure 4.*** Demonstration of hydrogel-patterned microcapsules for practical use: a) SEM image showing the microcapsules and square hydrogel features; b) fluorescence optical micrograph showing the location of rhodamine B after one stretching event. Mechanical stimulation is applied by c) opening and d) closing of the hand.

microcapsules can be used as a strain-regulated patch: the motion of gripping and stretching released molecules in the same way as shown in Figure 4b.

In summary, we have fabricated arrays of microcapsules by transferring buckled polymer patterns onto an elastomer substrate. As strain was applied to the elastomer substrate, the volume of the microcapsules decreased correspondingly. Upon mechanical stretching, the microcapsules pumped out preloaded molecules. The amount of molecules released at each pumping event was adjusted by the degree of strain. We also demonstrated a strain-sensitive patch that made use of hydrogel patterns fabricated on the arrayed microcapsules.

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