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A controlled biochemical release device with embedded nanofluidic channels

Haifeng Yang,† Wei Hong,‡ and Liang Dong§
†Department of Electrical and Computer Engineering, Iowa State University, Ames, Iowa 50011, USA
‡Department of Aerospace Engineering, Iowa State University, Ames, Iowa 50011, USA

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A controlled release device is developed by embedding nanofluidic biomolecule reservoirs into a polymer network of a stimuli-responsive hydrogel. The reservoirs are made of liquid core-polymer shell nanofibers using co-electrospinning. The mechanism of controlled release is based on buckling instability of the polymer shell under combined axial and radial compression, caused by volume changes of hydrogel responding to a specific stimulus. The device decouples releasable biomolecules from a hydrogel polymer matrix, avoiding chemical interactions between biomolecules and hydrogel polymer chains, and thus, alleviating nontrivial chemical and biological engineering design of hydrogel formulations. Temperature-sensitive hydrogel is used as a model hydrogel. © 2012 American Institute of Physics. [http://dx.doi.org/10.1063/1.4704143]

Controlled release of active molecules (e.g., drug, gene, DNA, protein, and chemical agent) is highly desired for many applications in such diverse fields as pharmaceutical, agricultural, cosmetic, and food industries.1–3 Polymeric micro/nanostructures such as spheres, tubes, fibers, and membranes play important roles in encapsulating and releasing these biomolecules.4–8 Generally, biomolecules of interest are incorporated in either dissolved or dispersed form within a polymer matrix, and then, gradually diffuse out in a controlled manner by chemical and biological interactions between the polymer and the body environment. This type of controlled release devices often has no complex structures nor requires connecting to an external molecule source.4–8 The other type of release devices is formed using micro-electro-mechanical systems (MEMS) technology. They can be reloaded with biomolecules of interest and can accurately control molecule release using relatively complex MEMS structures.9 The controlled release device studied in this paper falls in the former category.

Stimuli-responsive hydrogels are smart materials that can expand and contract, responding to environmental stimuli such as glucose, antigen, pH, temperature, light, electric field, and ionic strength.10 Research and development of controlled release devices based on stimuli-responsive hydrogels have been attracting much attention.11–17 However, almost all existing hydrogel-based release schemes require chemically incorporating releasable molecules into hydrogel delivery matrices by molecular binding. Liberation of entrapped molecules relies on swelling polymer chains as hydrogels undergo a responsive swelling-driven phase transition, or cleaving polymer chains via hydrolytic degradation or enzyme attack.15 Therefore, to realize controlled release of molecules from hydrogels, many factors and their interplays have to be taken into account, including polymer-molecule binding affinities and interactions, destruction of labile covalent bonds, release kinetics of entrapped molecules within hydrogel matrices, and swelling rate of polymer networks.16,17 This may pose complexity and difficulty in designing hydrogel pharmacological formulations and associated delivery micro/nanocapsules. Electrospinning is a simple, effective, and versatile method for producing nanofibers from polymers or polymer blends. It utilizes a high electric field to draw a charged polymer solution out of a metallic needle into a liquid jet. The jet undergoes thinning, bending, and stretching in air. Finally, nanofibers fall onto a collector. Co-electrospinning is a relatively new technology with a co-annular nozzle, for fabricating complex nanofibers encasing materials such as polymer and liquid crystal within a polymer shell.18,19 New applications of co-electrospun nanofibers are expanding. For example, we recently developed flexible light-emitting nanofibers by encapsulating liquid metal into a polymer sheath of organic electroluminescent materials.20

In this paper, we report a controlled biochemical release device embedding nanofluidic channels into a polymer network of a stimuli-responsive hydrogel (Fig. 1(a)). The nanofluidic channels serve as biomolecule reservoirs and are formed by multiple liquid core-polymer shell nanofibers. The core layer of the nanofibers contains an aqueous solution with biomolecules of interest. The outer layer is made of a hydrophobic polymer shell, functioning as a barrier to minimize lateral leakage of encapsulated biomolecules. The nanofibers are fabricated using co-electrospinning and then are embedded into a stimuli-responsive hydrogel membrane. Two ends of the nanofibers are open. Our hypothesis for controlled release of the device is based on buckling instability of the polymer shell of the nanofibers. Briefly, interactions between the hydrogel and a specific stimulus cause to change physical volume of the hydrogel. As a result, the embedded nanofibers carry a large compressive stress in both axial and radial directions, causing buckling of the shell of the nanofibers and extrusion of the encapsulated biomolecules. The present device decouples releasable biomolecules from a hydrogel polymer matrix, avoiding chemical interactions between the biomolecules and the hydrogel polymer chains, and thus, alleviating nontrivial chemical and biological

†Author to whom correspondence should be addressed. Electronic mail: ldong@iastate.edu. Telephone: 515-294-0388. Fax: 515-294-8432.

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engineered design of hydrogel formulations. Therefore, this method can make it easier and more accurate to tune and optimize release characteristic of the device.

To demonstrate the mechanism, N-isopropyl acrylamide (NIPAAm) temperature-sensitive hydrogel is used as a model hydrogel, which expands at low temperatures and shrinks at high temperatures. Hydrophobic poly (D, L-lactide) (PDLA; PDLA-to-chloroform weight ratio = 1:8) and aqueous Brilliant Blue G (BBG, 1 mg/ml) solution are used as the polymer shell material and inner core liquid, respectively, of the nanofibers. Since interaction between water and PDLA is thermodynamically unfavorable, possible lateral leakage of BBG molecules through the shell is significantly reduced. Figures 1(b)–1(d) show the brief device fabrication processes for the device: co-electrospinning liquid core-polymer shell nanofibers (b); flowing hydrogel solution into nanofiber interstitials and photopolymerization of hydrogel (c); cutting a strip of hydrogel membrane embedding nanofibers (d). (e) Fluorescent image for part of the fabricated device (green: hydrogel; red: nanofibers).

implemented through a user subroutine. We assume the hydrogel to be in equilibrium with pure solvent and execute a static analysis disregarding the drug flow in the core. The Flory-Huggins parameter $\chi$ is gradually increased from 0.1 to 0.5 to model the effect of the temperature-induced phase transformation. The increased hydrophobicity causes the hydrogel to shrink.

For simplicity, we neglect the interaction between nanofibers and only look at a single nanofiber in a large piece of hydrogel. The cross-sectional geometry of nanofiber is set to that measured, and the elastic modulus of PDLA is set to be 1000 times that of dry NIPAAm. The initial water concentration is set to be 97.5 vol. %. The simulated deformation pattern is shown in Fig. 2. During the initial stage of deswelling, the nanofiber deforms uniformly (Figs. 2(a) and 2(b)). When $\chi$ further increases beyond a critical value, the uniform deformation loses stability, and the nanofiber buckles. The initial buckling is close to the Euler buckling of a beam, but as the amplitude increases, the circular cross section collapses (Fig. 2(c)). The cross-sectional images shown in Figs. 2(d) and 2(e) illustrate this change. Before the onset of instability, the cross section of the nanofiber remains circular, with the diameter slightly increases due to the Poisson effect. As a result, the internal volume of the nanofiber is hardly changed, and the liquid drug is not released except by diffusion. It is shown that, after buckling, the cross section of the nanofiber is flattened, and the internal volume greatly reduced. The drug content is thus squeezed out from the nanofiber. Similar to the wrinkles in a hard-film-soft-substrate system, the wavelength of buckling is set by the nanofiber geometry and the stiffness ratio between the nanofiber and the hydrogel membrane.

As a release indicator, BBG has a characteristic absorption peak at the wavelength of 600 nm. BBG release from the fabricated device is determined by measuring changes in absorption intensity with a spectrometer (2800 UV/VIS, UNICO). A nanofiber-hydrogel device is placed on the bottom of a quartz cuvette (BrandTech Scientific) containing deionized water. Local temperature of the cuvette is

![FIG. 1. (a) Schematic for structure and mechanism of the controlled release device. Fabrication processes for the device: co-electrospinning liquid core-polymer shell nanofibers (b); flowing hydrogel solution into nanofiber interstitials and photopolymerization of hydrogel (c); cutting a strip of hydrogel membrane embedding nanofibers (d). (e) Fluorescent image for part of the fabricated device (green: hydrogel; red: nanofibers).](http://apl.aip.org/)
controlled by a Kapton heater, a Type-K thermocouple, and a thermostat. Prior to each spectroscopic measurement, the liquid in the cuvette is stirred gently for several seconds using a glass rod, to obtain a uniform distribution of BBG molecules within the cuvette. Each measurement cycle takes about 8 s.

Figures 3(a) and 3(b) demonstrate temperature response of the device to a temperature excitation. Here, the device temperature is increased from room temperature (22°C at \( t = 1 \) h) and stabilized at 26°C after 110 s, and then, it is held for 40 s before the heater is turned off (upper panel in Fig. 3(c)). About 10 s after the temperature stabilization, the hydrogel starts to shrink and then stops in 10 s. BBG release increases rapidly from 9.1 to 16.3 wt. % of the total loading amount in 8 s (Fig. 3(a), and lower panel in Fig. 3(c)). To confirm the role of the hydrogel in controlling the molecule release, two control experiments (controls “A” and “B”) are conducted. The control “A” device is identical to the actual device having both hydrogel and nanofibers, but operates at a constant temperature of 22°C. Thus, molecule release is governed by molecular concentration difference induced entropic driving force. It is obvious that the release profile of the actual device deviates from that of the control “A” device. We note that increasing temperature can not only trigger hydrogel contraction, but also cause to elevate diffusion rate of BBG from the core. It is thus necessary to find out how each of the two consequences contributes to regulating the release profile of the actual device. The control “B” device only has nanofibers but does not have surrounding hydrogel. Under the same temperature activation (upper panel in Fig. 3(c)), BBG release increases only slightly from 9.1 to 10.6 wt. % of the total loading amount. This release counts only a small portion of the total release from the actual device (from 9.1 to 16.3 wt. %). Response of the device to a different temperature excitation is demonstrated in supplementary material. Therefore, it is confirmed that the hydrogel volume change dominates the modulation of the molecule release in the present device.

We believe that the release action is mainly caused by buckling instability of the PDLA shell of the nanofibers. As shown in Fig. 3(c), almost no BBG molecule is released after temperature increases, until a certain delay after which a large amount of drug is released. The delay followed by sudden release is an evidence of the buckling mechanism. Due to the huge difference in stiffness between the PDLA and the NIPAAm hydrogel, the shrinkage of the hydrogel initially would not induce a large deformation in the nanofibers. Instead, a hoop stress is developed in the hydrogel surrounding each fiber. With the thickness of the shell comparable to its inner radius, the radial collapse of the cylindrical shell may seem unlikely if only the hoop stress is present. In this system, the nanofibers also carry a large compressive stress in the axial direction, as shown in Fig. 2(b). The combined axial and radial compression is expected to cause the buckling of the PDLA shells.

Figure 4(a) (left axis) displays net BBG releases from multiple similar devices under various temperature excitations. Each nanofiber-hydrogel device is heated up from 22°C (at \( t = 1 \) h) to a specific higher temperature. BBG
release is monitored 10 s after a higher temperature is stabilized. The result shows that the devices with large temperature rises release more BBG than those with small temperature rises. A significant BBG increase occurs between 30 and 35 °C. A primary reason behind the observation is that the volume phase transition point of the NIPAAm hydrogel is around 32 °C, near which the hydrogel shrinks rapidly. Volume response of the hydrogel membrane embedding the nanofibers is shown in Fig. 4(a) (right axis).

Figure 4(b) demonstrates real-time regulating the release profile of a nanofiber-hydrogel device by applying multiple temperature excitations at different time instances. Here, the device is excited from 22 to 26 °C at t = 1 h, from 22 to 28 °C at 2 h, from 22 to 30 °C at 4 h, and from 22 to 32 °C at 6 h, giving rise to release 7.2, 10.5, 15.1, and 10.4 wt. %, respectively, of the total loading amount, whereas a control device releases 1.5, 1.9, 2.3, and 3.8 wt. %, respectively, under the same conditions. The result not only confirms further that the hydrogel functions to squeeze the encapsulated molecules out of the nanofibers, but also, more importantly, demonstrates the capability of tuning the release characteristic in a real-time manner.

To examine how the length of the nanofibers L affects a time gap τ between observing hydrogel contraction and observing abrupt molecule release, we fabricate five nanofiber-hydrogel devices with different L. As L increases from 6 to 18 mm (Fig. 4(c)), τ increases from 8 to 41 s under the same temperature excitation (22 → 26 °C at 1 h). Also, the increasing rate of τ is found to increase with increasing L. A possible explanation is as follows. As the nanofibers are being deformed by shrinking hydrogel, the encapsulated molecules in the liquid core experience acceleration. When the short nanofibers are used, BBG molecules in the deep central region of the liquid core can leave the nanofibers before the hydrogel contraction is completed. But, this is not the case when the long nanofibers are used: after the hydrogel contraction is completed, BBG molecules have not been away from the nanofibers. They continue moving inside the nanofibers mainly by inertia, but not by a squeezing force. Due to lack of further acceleration, a longer time is required for the encapsulated molecules to leave the nanofibers.

The present work has demonstrated integrating co-electrospun nanofluidic channels into stimuli-sensitive hydrogels to realize controlled release of biomolecules. The device architecture allows isolating releasable molecules from responsive polymer matrices and, thus, minimizing complex chemical and biological engineering design effort of hydrogel formulations. The co-electrospinning process allows for flexible tuning of materials and dimensions of the polymer shell and liquid core of nanofibers. Also a wide variety of materials (e.g., neural probes, plastic, silicon) may be chosen to collect nanofibers. Further elaboration of the controlled release technology is possible by taking the following efforts. First, the present device is obtained by cutting from a hydrogel membrane embedding core-shell nanofibers. To accurately control device dimensions, selective nanofiber patterning techniques can be adopted to pattern as-deposited nanofibers. Second, the encapsulated molecules in the nanofibers initially diffuse out through the two side openings of the nanofibers. This issue could be alleviated by using an appropriate polymer-based molecule carrier in the core of the nanofibers. Finally, the simulation result presented here serves the purpose of demonstrating the mechanism. With more detailed material models, dynamic release process may be simulated. Nevertheless, by employing other specific stimuli-responsive hydrogels into the present device architecture, this approach can potentially herald a possible solution for controlled release of various biological species and chemical agents.

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\[ V = \frac{1}{2} \rho \int \mathbf{r} \cdot \mathbf{F} - \mathbf{F} \cdot \mathbf{r} \, du \]


[See supplementary material at http://dx.doi.org/10.1063/1.4704143 for showing materials and preparations of the device and an additional exam-
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\[ E = \frac{1}{2} \rho \int \mathbf{r} \cdot \mathbf{F} - \mathbf{F} \cdot \mathbf{r} \, du \]