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Controlling Release From pH-Responsive Microcapsules

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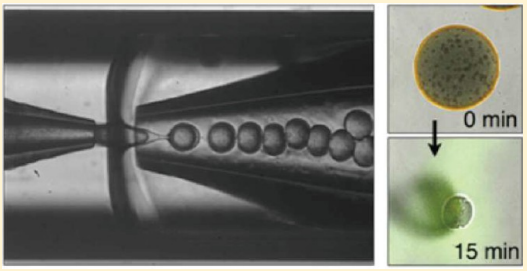
ABSTRACT: We report a microfluidic approach to produce monodisperse pH-responsive microcapsules with precisely controlled release behavior. The solid microcapsule shells are composed of a biocompatible pH-responsive polymer and robustly encapsulate an active material; however, when exposed to a trigger pH, the shells degrade and ultimately release the microcapsule contents. We control the trigger pH by using polymers that dissolve at different pH values. We independently control the time at which the microcapsule contents are released by carefully controlling the shell thickness. Moreover, we independently control the rate at which the encapsulated contents are released by making hybrid shells composed of a mixture of a pH-responsive polymer and varying proportions of another, solid, pH-unresponsive polymer. This enables us to achieve monodisperse microcapsules that robustly encapsulate an active material, only releasing it when exposed to a desired pH, after a prescribed time delay, and at a prescribed rate.



INTRODUCTION

Microcapsules are promising candidates for encapsulating, delivering, and controllably releasing many technologically important actives, including agricultural chemicals,[1,2] surfactants for enhanced oil recovery, cosmetic components,[3,4] food additives,[5−7] and pharmaceuticals.[8−13] These applications often require the microcapsules to release their contents only after exposure to an external stimulus;[14−30] one important example is a change in pH. Moreover, in many cases, the time delay between exposure and release, as well as the rate of release, must be carefully controlled. Microcapsules that release their contents when exposed to a range of stimuli can be fabricated using a variety of conventional techniques, such as spray drying,[31] coextrusion,[32,33] interfacial polymerization,[34,35] or phase separation.[36] Unfortunately, the highly variable shear inherent in these approaches typically results in microcapsules with polydisperse sizes and structures, and consequently, poorly controlled encapsulation and release characteristics, even within the same batch. Microfluidic technologies offer a route to overcoming these difficulties and can be used to fabricate a wide variety of monodisperse microcapsules.[18,37−42] However, controlling the kinetics of release from such microcapsules remains challenging; this severely limits their use in many practical applications.

In this paper, we report a microfluidic approach to produce monodisperse pH-responsive microcapsules with precisely controlled release properties. We use a capillary microfluidic device to prepare water-in-oil-in-water (W/O/W) double emulsion drops as templates;[43−48] the middle oil phase is a solution of a pH-responsive polymer, which forms a uniform solid shell upon dissolution of the solvent into the outer phase. When exposed to a trigger pH, this shell dissolves at a constant rate, ultimately releasing the microcapsule contents. By using polymers that respond to different pH values, we fabricate microcapsules that respond to either acidic or basic conditions. We exploit the exquisite flow control afforded by microfluidics to control the shell thickness and, consequently, the time delay before the contents are released. Moreover, we prepare hybrid microcapsules with shells composed of a mixture of a pH-responsive and a pH-unresponsive polymer; when exposed to a trigger pH, these shells dissolve only at their pH-responsive regions. Thus, by varying the proportions of the different polymers, we independently control the rate at which the microcapsule contents are released. This approach enables us to achieve monodisperse microcapsules that robustly encapsulate their contents, only releasing them when exposed to a desired pH, after a prescribed time delay, and at a prescribed rate.

EXPERIMENTAL DETAILS

We use a glass capillary microfluidic device to prepare monodisperse W/O/W double emulsion drops as templates to form microcapsules.[43] The device consists of two tapered cylindrical capillaries inserted into the opposite ends of a square capillary, whose inner dimension is slightly larger than the outer diameter of the cylindrical capillaries, as illustrated by the optical micrograph in Figure 1a. This configuration enables us to accurately align both cylindrical capillaries. We use the left cylindrical capillary to inject the innermost aqueous phase, a 5 wt % aqueous solution of polyvinyl alcohol (PVA) of molecular weight 13 000−23 000, seeded with a small amount of 6-nm-diameter quantum dots for flow visualization. We treat this capillary with *n*-octadecyltrimethoxysilane; this renders its surface hydrophobic, preventing wetting of the aqueous phase on the capillary wall. To fabricate solid microcapsules, we use a middle oil phase composed of a 5−15 wt % solution of an anionic diblock copolymer of acrylic acid and methyl methacrylate (PAA-*b*-PMMA) in a mixture of 70 vol% chloroform and 30 vol% tetrahydrofuran (THF).[23] We inject this oil from the left, forcing it to flow in the same direction as the inner aqueous phase, through the interstices between the left cylindrical

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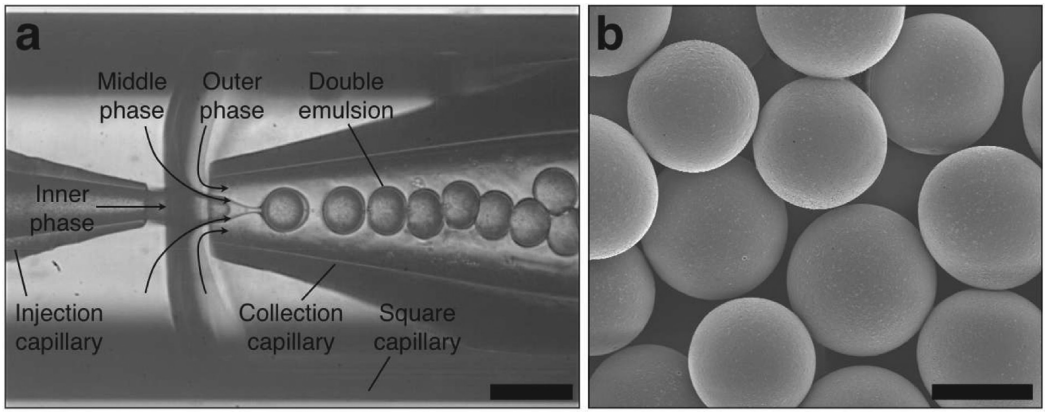

Figure 1. (a) Optical micrograph of a glass capillary microfluidic device as it produces monodisperse double emulsions. Scale bar is 250 μm. (b) Scanning electron microscope micrograph of monodisperse, uniform, solid microcapsules formed after evaporation of the solvent from the middle phase of the double emulsion drops. Scale bar is 100 μm.

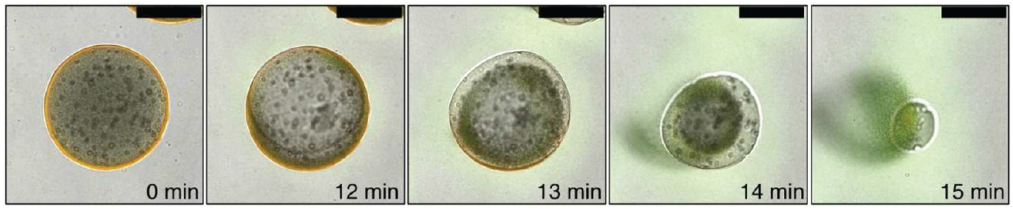

Figure 2. Optical micrographs showing the degradation of the 500-nm-thick shell of a microcapsule, leading to the release of an encapsulated dye starting at 12 min (green; fluorescence micrograph superimposed). The microcapsules also encapsulate, and subsequently release, polystyrene particles used for enhanced visualization (gray). Scale bar is 100 μm. Time stamp shows time elapsed after pH is raised to 9.

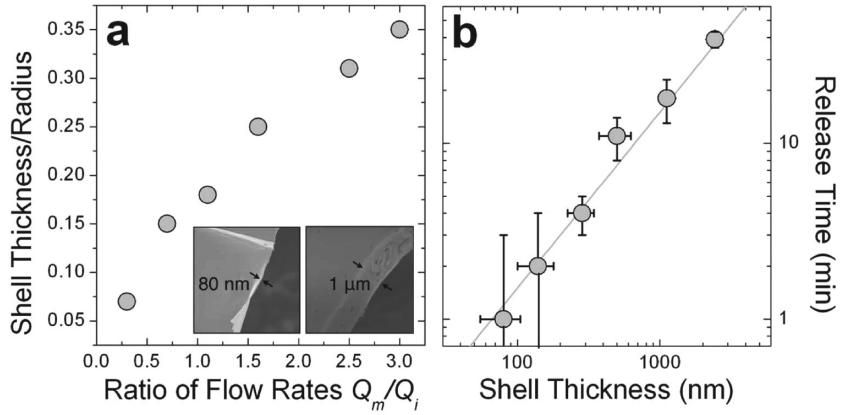

Figure 3. (a) Ratio of microcapsule shell thickness to shell radius, measured using scanning electron microscopy, increases with increasing ratio of middle phase flow rate Q_m to inner phase flow rate Q_i. Example scanning electron micrographs for thin and thick shells are shown in the inset. (b) Time delay before release begins, quantified using fluorescence microscopy of microcapsules encapsulating a fluorescent dye, increases with increasing shell thickness, for shells triggered at pH = 9; gray line shows linear relationship. Vertical error bars show standard deviation in measured release time, while horizontal error bars show standard deviation in shell thickness of each batch.

capillary and the square capillary. The outermost aqueous phase is a 10 wt % aqueous solution of PVA containing 15 wt % THF; we inject it from the right, forcing it to flow in the opposite direction, through the interstices between the right cylindrical capillary and the square capillary. We operate this hydrodynamic focusing geometry in the dripping regime, causing the inner and middle phases to break up at the orifice of the right cylindrical capillary; this forms monodisperse W/O/W double emulsions, as shown in Figure 1a.

We use the right cylindrical capillary to collect these double emulsion drops; this capillary is treated with 2-(methoxy-(polyethyleneoxy)propyl)trimethoxysilane, rendering its surface hydrophilic and preventing wetting of the middle oil phase on the capillary wall. After the double emulsion drops are collected, the solvent in the middle oil phase slowly diffuses into the outer continuous phase; this forces the PAA-*b*-PMMA to precipitate. Within 1 h, this forms a uniform solid shell of radius ≈69 μm, as exemplified in Figure 1b. We wash the monodisperse microcapsules thus formed with water, adjusted to have pH = 6, three times to remove any residual solvent or any surfactant from the continuous phase. We verify that the microcapsule shells are solid by crushing the microcapsules between two glass slides, as well as by imaging the microcapsules directly using scanning electron microscopy. To study the ability of the microcapsules to encapsulate an active material, we encapsulate either 6-nm-diameter quantum dots or a fluorescent polymer (6 kDa FITC–dextran), in the microcapsule cores, and measure the change in the fluorescence intensity of the cores over time. After 30 days, we find that only 3% of the quantum dots leak from the microcapsule cores; by

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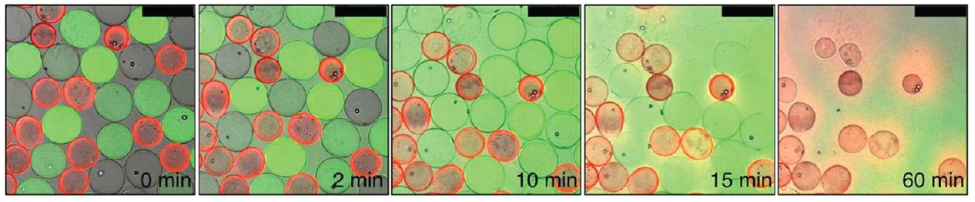

Figure 4. Optical micrographs showing the release, starting at 2 min, of an encapsulated dye from microcapsules with 500-nm-thick shells (green; fluorescence micrograph superimposed). A second encapsulated dye is then released, starting at 15 min, from microcapsules with 4-μm-thick shells (red; fluorescence micrograph superimposed). Scale bar is 250 μm. Time stamp shows time elapsed after pH is raised to 9.

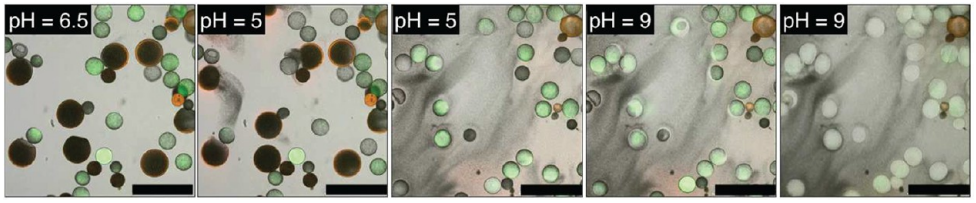

Figure 5. Optical micrographs showing the release of an encapsulated dye only from acid-responsive DMAEMA-BMA-MMA microcapsules (yellow; fluorescence micrograph superimposed) when the pH is reduced to 5 (second and third frames). A second encapsulated dye (green; fluorescence micrograph superimposed) and 1 μm polystyrene particles (gray) are then released from base-responsive PAA-*b*-PMMA microcapsules when the pH is increased to 9 (fourth and fifth frames). Scale bar is 500 μm. The shells of both types of capsules are 500 nm thick.

contrast, we find that 18% of the smaller FITC−dextran leaks from the microcapsule cores.

RESULTS AND DISCUSSION

Controlling Release Time. When exposed to a basic pH > 7, the polymer chains making up the shells become highly charged and repel each other.[23] This causes the microcapsule shells to dissolve at a constant rate, starting at their exteriors; after a time delay of several minutes, the shells become fully dissolved and the microcapsules release their contents, as shown in Figure 2. We expect microcapsules with thicker shells to take longer to fully dissolve and ultimately release their contents; thus, to control the time of release, we exploit the precise flow control afforded by microfluidics to prepare microcapsules of the same outer radius but with different shell thicknesses. We do this by varying the flow rates of the inner and middle phases, Q_i and Q_m, respectively, while maintaining their sum, and the flow rate of the outer phase, Q_o, at constant values of 1.2 mL/h and 6.0 mL/h, respectively. Crucially, the thickness of the middle phase of each double emulsion drops, and consequently the thickness of the solid shell formed from it increases with increasing Q_m/Q_i, as shown in Figure 3a. To quantify the release kinetics for microcapsules of different shell thicknesses, we monitor individual microcapsules using fluorescence microscopy, measuring the time between initiation of a trigger through exposure to a pH = 9 and the beginning of the release from their interiors.[49] The time delay increases linearly with increasing shell thickness, varying from just a minute up to tens of minutes, as shown in Figure 3b; this is consistent with our expectation. We note that this approach is general, and the release can be triggered by any pH larger than 7; we demonstrate this concept by choosing a trigger pH of 9. The release kinetics may depend on the exact trigger pH used.

By fabricating and mixing varying amounts of different populations of capsules, each characterized by a different shell thickness, we can precisely control the distribution of release times over a range spanning 1 min to nearly 1 h. This enables us to program sequential release from different microcapsules; to illustrate this, we fabricate and mix two different populations of microcapsules, having either thin 500 nm shells or thick 4 μm shells. We distinguish the two populations by encapsulating a green and a red dye within the microcapsules having thin and thick shells, respectively (first frame, Figure 4). We increase the pH of the continuous phase to 9, forcing the shells to dissolve. After 2 min, the microcapsules with thin shells release their contents; in contrast, the microcapsules with thicker shells continue to stably encapsulate their contents, as shown in the second and third frames of Figure 4. These subsequently release their contents after an additional 13 min have passed, as shown in the last two frames of Figure 4. These results demonstrate that varying the microcapsule shell thickness provides a straightforward means of programming sequential release at different times.

Controlling Release pH. This experimental approach can be used to trigger release at a range of different pH conditions. To illustrate its generality, we apply the same microfluidic device but use a different middle oil phase; this enables us to prepare microcapsules that release their contents under acidic conditions. The oil phase is an 8 wt % solution of a cationic triblock copolymer of poly(*n*-butyl methacrylate-(2-dimethylaminoethyl)-methacrylate-methyl methacrylate) (DMAEMA-BMA-MMA) in a mixture of 70 vol% chloroform and 30 vol % THF.[50] Similar to the previous case, after the double emulsion drops are formed and collected, the solvent in the middle oil phase slowly diffuses into the continuous phase; this forces the polymer to precipitate, forming a uniform solid shell. We again study the ability of the microcapsules to encapsulate an active material by encapsulating either quantum dots or FITC−dextran in their cores. After 30 days, we find that only 5% of the quantum dots leak from the microcapsule cores; by contrast, we find that 15% of the smaller FITC−dextran leaks from the microcapsule cores.

In contrast to the PAA-*b*-PMMA case, the DMAEMA-BMA-MMA polymer chains become highly charged only under acidic conditions; consequently, the microcapsule shells thus formed dissolve and release their contents only for pH < 6.[51,52] We are therefore able to prepare microcapsules that very stably

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encapsulate their contents and only release them when exposed to either acidic or basic conditions.

This experimental approach enables us to program the sequential release of different actives upon exposure to different pH conditions; to illustrate this, we fabricate and mix two different populations of acid-responsive and base-responsive microcapsules. We distinguish the two populations by encapsulating a green dye within the base-responsive PAA-*b*-PMMA microcapsules, and a yellow dye, along with 1 μm polystyrene particles, within the acid-responsive DMAEMA-BMA-MMA microcapsules (first frame, Figure 5). Both populations of microcapsules are stable in water adjusted to have pH = 6.5. We then decrease the pH of the continuous phase to 5; while the base-responsive microcapsules remain stable, the acid-responsive microcapsules quickly release their contents, as shown in the second and third frames of Figure 5. We subsequently increase the pH of the continuous phase to 9; this forces the base-responsive microcapsules to also release their contents, as shown in the last two frames of Figure 5. These observations demonstrate that varying the microcapsule shell composition provides a straightforward means of programming sequential release at different pH. We note that this approach is general, and the release can be triggered by any pH smaller than 6; we demonstrate this concept by choosing a trigger pH of 5. The release kinetics may depend on the exact trigger pH used.

Controlling Release Rate. The pH-responsive polymers making up the microcapsule shells phase separate when solidified in the presence of another, pH-unresponsive, polymer. We exploit this effect to prepare hybrid microcapsules that, when exposed to a trigger pH, selectively dissolve only at parts of their shells. We again apply our microfluidic approach, using a different middle oil phase; we use a mixture of 0−20 wt % of the base-responsive PAA-*b*-PMMA with 80−100 wt % pH-unresponsive ethylene glycol phenyl ether methacrylate monomer, 0.5 wt % 1,6- hexanediol dimethacrylate cross-linker, and 0.2 wt % 2-hydroxy-2-methylpropiophenone photoinitiator. Immediately after the double emulsion drops are formed, they are irradiated with UV light; this photopolymerizes the pH-unresponsive polymer in the middle oil phase.[53−56] We then collect the drops in water adjusted to have pH = 6. Similar to the previous case, the pH-responsive polymer precipitates, completing the formation of a uniform, solid, hybrid shell. We again study the ability of the microcapsules to encapsulate an active material by encapsulating either quantum dots or FITC−dextran in their cores. After 30 days, we find no measurable leakage of the quantum dots from the hybrid microcapsule cores; by contrast, we find that only 6−11% of the smaller FITC−dextran leaks from the hybrid microcapsule cores.

When these hybrid microcapsules are exposed to a trigger pH > 7, only the base-responsive portions of their shells dissolve, forming holes; this is illustrated by the schematics and scanning electron micrographs shown in the top panel of Figure 6. This selective dissolution reflects the phase separation between the pH-responsive and pH-unresponsive polymers in the microcapsule shells. The size of the holes formed increases with increasing PAA-*b*-PMMA content, as shown in Figure 6; this presumably increases the permeability of the degraded shell and hence the rate at which it releases its contents.[57] We test this hypothesis by fabricating a hybrid capsule of varying PAA-*b*-PMMA content and use confocal fluorescence microscopy to monitor the dynamics of their release when exposed to a trigger pH. Importantly, we find that the release rate increases with

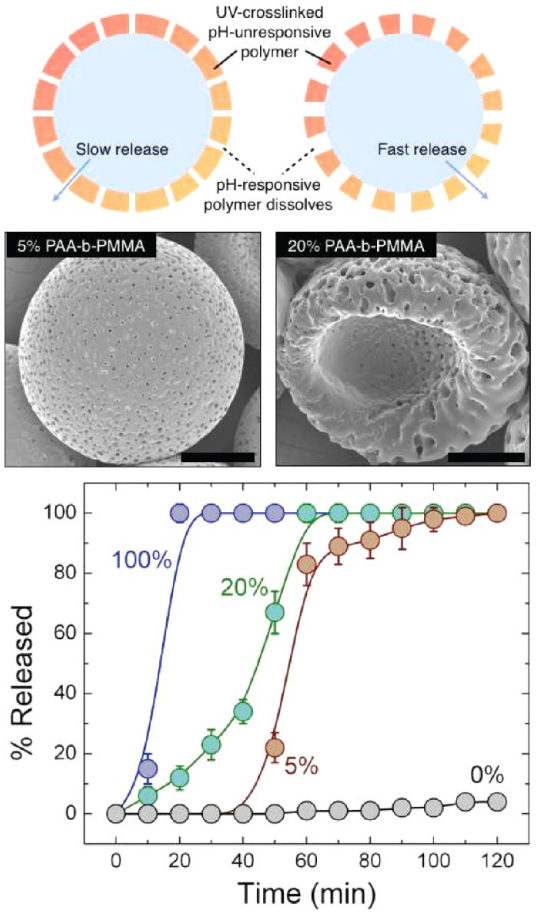

Figure 6. (Top) Schematic representation and (middle) scanning electron microscope micrographs of hybrid microcapsules with holes formed in their shells after degradation in an unfavorable pH = 8.5. The size of the holes increases with increasing pH-responsive PAA-*b*-PMMA content in the shell. Scale bars are 80 μm. Shell thickness is 2.4 μm for both microcapsules. (Bottom) Amount of encapsulated material released, quantified by monitoring the relative intensity in the core of microcapsules encapsulating a fluorescent dye, increases with time; capsules are triggered at pH = 9. The rate at which the material is released increases with the PAA-*b*-PMMA content of the shell (numbers next to each curve). Vertical error bars show standard deviation of measured intensity in each batch, at each time point.

increasing PAA-*b*-PMMA content, as shown by the different curves in Figure 6. These observations confirm that the microcapsule release rate can be independently tuned by the composition of the hybrid shell.

■ CONCLUSIONS

In this work, we report a microfluidic approach to produce double emulsion-templated monodisperse pH-responsive microcapsules with precisely controlled release properties. By controlling the shell thickness, we control the amount of time required to fully dissolve the shell and hence the time at which the microcapsule contents are ultimately released. By using different pH-responsive polymers to form the microcapsule shell, we control the trigger pH. This can range from highly acidic conditions, such as those encountered in the human stomach, or basic conditions, such as those encountered in parts of the small intestine and the colon.[58] The pH-responsive polymers we use are enteric and biocompatible; thus, our microcapsules may be promising candidates for the delivery of

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pharmaceutical products to different areas of the human digestive system. Moreover, by varying the fraction of the microcapsule shell made up of pH-responsive polymer, we independently control the shell permeability and hence the rate at which each microcapsule releases its contents. This approach is general and can be applied to a wide range of polymers. We note that the pH-unresponsive polymer we use here is not biocompatible; further work is therefore required to develop fully biocompatible hybrid microcapsules.

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Author Contributions

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Notes

The authors declare no competing financial interest.

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