Soft Matter

PAPER

Mechano-responsive microcapsules with uniform, thin shells

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Capsules often prolong the shelf-life of active ingredients, such as many drugs, food additives, or cosmetic substances, because they delay oxidation of these substances or prevent their reactions with molecules contained in the surrounding. If appropriately designed, these capsules can offer an additional benefit: they allow close control over the timing and location of the release of active ingredients. To take advantage of these features, capsules must possess shells whose thickness and composition is well-defined. However, the shell thickness of capsules often varies considerably even within a single capsule, thereby hampering good control over the release kinetics of encapsulants. These variations can be reduced, and hence the degree of control over the release kinetics increased, if shells are made thin. Unfortunately, the controlled fabrication of mechanically stable microcapsules with well-defined sub-µm thick shells is difficult. Here, we introduce a method to fabricate capsules with uniform, semi-permeable shells whose thickness is as low as 400 nm. This is achieved using water-oil-water double emulsions with 800 nm thick shells as templates to fabricate capsules with uniform 400 nm thin shells. These shells occupy less than 2% of the capsule volume, thereby minimizing their footprint. Despite of their thin shells, these capsules are mechanically robust: They withstand pressures up to 1.3 MPa without deformation and remain intact if exposed to pressures up to 2.75 MPa. Moreover, while they are permeable towards water, they retain low molecular weight encapsulants even if dried and re-dispersed. The thin shells of the capsules open up new possibilities to use them to functionalize materials with at least one dimension that is small, such as coatings, where thick shells introduce defects, or as building blocks of new types of functional materials.

Introduction

Microcapsules are widely used for example in pharmacy,[1,2] food,[3–5] and cosmetics,[6,7] to delay the degradation of reagents, protect their interactions with substances contained in the surrounding media, or to control the timing and location of their release.[8–11] Ideally, those capsules are impermeable to encapsulants during storage and when applied, release their content on demand.[12] Capsules are often produced through spray-drying[13] or from single emulsion drops where the surface of drops is solidified for example through interfacial polymerization[14,15] or phase separations.[16] These methods typically offer a limited control over the thickness of capsule shells, thereby compromising the control over the timing of the release of encapsulants.[17–20] Capsules can also be produced from double emulsion drops by solidifying their shells.[21,22] The thickness of the so-formed capsule shells depends on the composition and dimensions of the double emulsion shells. Double emulsions with well-defined dimensions can be produced with microfluidic devices; these drops have diameters ranging from 60 to 700 µm and shell thicknesses varying between 2 and 140 µm.[22–26] The shells of these capsules occupy between 20 to 85% of the total capsule volume, thereby limiting the relative concentration of encapsulants contained in them. The fabrication of capsules with thick shells from double emulsion drops comes at an additional cost: While the average thickness of these capsule shells is well-defined, the local shell thickness varies considerably within each capsule. This difference can be assigned to variations in the shell thickness of double emulsion drops that are caused by the density difference between the liquid that forms the innermost drop and the liquid that constitutes the outermost drop. This density difference causes an offset of the two drop centers such that the shells are very thin on one side of the double emulsion drop whereas they are very thick on its opposite side.[23] This heterogeneity in shell thickness compromises the control over the diffusion time of encapsulants across the shell and hence, the control over the kinetics of the diffusion-limited release.[27–29]

This potential limitation can be alleviated if capsules are composed of a material that has a low affinity to the encapsulants. In most cases, encapsulants are either hydrophilic or hydrophobic and hence have a low affinity towards fluorinated materials. As a result of the low affinity, capsules with shells composed of perfluoropolyethers retain more than 98% of low molecular weight encapsulants, such as Allura Red and $CaCl_2$, over a period 4 of weeks, even though the thinnest part of their shell is below 20 µm.[26] Additionally, fluorinated polymers typically have a low surface tension and a low friction coefficient.[30–32] These features, combined with

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their thermal and chemical stability and biological inertness,[33] render them attractive shell materials for capsules that display a low permeability towards hydrophilic and hydrophobic encapsulants. Hence, these capsules can be employed even in products encompassing a wide range of different solvents. However, the shells of these capsules occupy approximately 70% of their volume,[26] thereby limiting the concentration of reagents contained in them. Moreover, because perfluorinated polymers are chemically inert, they cannot easily be degraded such that residues of empty capsules remain in the final product. These residues can negatively affect the quality of the final products. For example, if capsules are used to functionalize coatings, they can change the surface roughness and optical appearance of coatings, thereby compromising their quality.

The volume fraction of capsules occupied by the shell can be reduced if they are produced from double emulsions with thin shells. These double emulsions offer an additional benefit: the thickness of their shells is much more uniform because the fluid flow in thin shells is limited by lubrication effects, thereby minimizing the offset between the centers of the innermost and the outer drops.[21,34,35] Double emulsions with thin shells can be assembled using dedicated microfluidic glass capillary devices.[12,36–40] However, the fabrication and operation of these devices is tedious. Double emulsions with thin shells can also be produced from standard double emulsions by reducing their shell thickness, for example if pushed through constrictions,[41] or processed with a microfluidic aspiration device that removes the vast majority of the fluid contained in the shells through shunt channels.[42] However, these double emulsions have never been employed as templates to produce polymeric capsules with thin, solid shells that display a low permeability towards encapsulants.

In this paper, we combine the benefit of the chemical inertness of perfluorinated polymers with the low footprint of capsules made from double emulsions with thin shells: We fabricate 63 µm diameter capsules with homogeneous fluorinated shells that are as thin as 0.4 µm, such that the shell occupies as little as 2% of the capsule volume. We investigate their mechanical properties and the permeability towards low molecular weight encapsulants and compare these parameters to those of capsules whose shells have an identical composition but are 25 times thicker. Despite of their thin shells, these capsules are mechanically robust: They can withstand pressures up to 1.3 MPa without buckling. When exposed to higher pressures or when dried, they buckle but remain intact such that the permeability towards low molecular weight encapsulants remains unchanged. Because perfluorinated shells have a low affinity towards hydrophilic additives, they retain more than 98% of the encapsulants with a molecular weight as low as 562 Da, such as Patent Blue V, for at least 4 weeks. However, when subjected to mechanical stress, they break, thereby releasing the encapsulants.

Materials and methods

Production of capsules with thin shells

The core of double emulsions is composed of 7.5 wt% poly(ethylene glycol) (PEG, M_w = 6 kDa) and 5 wt% partially hydrolyzed poly(vinyl alcohol) (PVA, M_w = 13 – 18 kDa); PVA is added to increase the stability of the double emulsion drops. The fluorophilic shell is made of 75 wt% monoacrylate, 1H,1H,7H-Dodecafluoroheptyl acrylate, 15 wt% 1H,1H,6H,6H-Perfluoro-1,6-hexyl diacrylate, and 10 wt% fluorinated oil, HFE 7500, that contains 2 % of a photoiniator, 2-Hydroxy-2-methylpropiophenone; the fluorinated oil is added to increase the contrast of the double emulsions in the optical microscope. As an outer phase, we employ an aqueous solution containing 10 wt% partially hydrolyzed poly(vinyl alcohol) (PVA, M_w = 13 – 18 kDa).

Double emulsion composition

Primary double emulsions are produced using PDMS-based microfluidic flow focusing devices that are fabricated through soft lithography.[43,44] To render the first junction fluorophilic, we treat the channel walls with HFE7500 containing 2 vol% heptadecafluoro1,1,2,2-tetrahydrodecyl trichlorosilane. To render the second junction, that is a 3D junction, hydrophilic, we treat the channel walls in this section with an aqueous solution containing 2 vol% Poly(diallyldimethylammonium chloride) (M_w = 200-350 kDa).

Microcapsule fabrication

To convert double emulsions into capsules, they are exposed to UV illumination for 5 min (Omnicure Series 1000 UV). The resulting microcapsules are washed with deionized water to remove residual PVA.

Imaging

Optical images are acquired with a Nikon Eclipse Ti-S Inverted Microscope and Scanning electron microscope images are acquired with a Zeiss FESEM Supra55VP using a secondary electron detection operated at an acceleration voltage of 1kV. Samples are deposited onto a one-side polished Si-wafer and coated with 10 nm of Platinium-Palladium coating to render it electronically conductive. UV-Vis spectra are acquired with a PerkinElmer UV/Vis Spectrometer Lambda 40.

Results and discussion

Production of capsules with thin shells

We employ water-oil-water double emulsions as templates to produce capsules; these double emulsions are fabricated using polydimethylsiloxane (PDMS) based microfluidic flow focusing devices whose main channel is 100 µm tall and 100 µm wide, as shown in Figure 1A.[45] To facilitate the fabrication of these double emulsions and to increase their stability, we add 7.5 wt% poly(ethylene glycol) (PEG) and 5 wt% poly(vinyl alcohol) (PVA) to their cores. The oil shell is composed of a fluorinated oil, HFE7500, that contains 75 wt% of a fluorinated monoacrylate, 15 wt% diacrylate, and a photoinitiator. These double emulsions are dispersed in an aqueous phase containing 10 wt% PVA. Double emulsions are formed in microfluidic flow focusing devices by injecting the inner and middle phases at a rate of $Q_i = Q_m = 500$ µL/h into the device.[45] The outer phase is injected at $Q_o = 4000$ µL/h. The resulting double emulsions have a diameter of $D = 80 \pm 0.8$ µm and a shell thickness of $t = 9.2 \pm 0.9$ µm such that the shell occupies 30% of the volume of the double emulsion.

To reduce the volume occupied by the shell and therefore to minimize the footprint of the capsules, the shells of the double emulsion templates must be made thinner. To reduce the shell thickness of double emulsions, we process them with a microfluidic aspiration device. The diameter of double emulsion drops that can be processed must be similar to the dimension of the main channel cross-section. In our case, this cross-section is 60 µm × 70 µm, enabling processing of double emulsions with diameters ranging from 60 to 80 µm. However, the diameters of double emulsions that can be processed with aspiration devices is by no means limited to this narrow range. If the dimensions of the main channel are adjusted, double emulsions with diameters ranging from 10 µm up to a few 100 µm can be processed with this technique. The main channel is intersected by many much smaller fluorophilic shunt channels that lead into two reservoirs, as shown in Figure 1C. Primary double emulsions are injected into the aspiration device at Q_{in} = 900 µL/h. To maximize the volume of the oil that shunt channels remove from the shells of double emulsions, we reduce the pressure in the reservoirs by retracting fluids at Q_w = 800 µL/h.[42] Due to the reduced pressure in the reservoir, some of the continuous phase is also removed through the shunt channels such that primary double emulsions are up-concentrated while they flow through the aspiration section. To increase the spacing between processed adjacent double emulsions after they exit the aspiration section, and thereby to facilitate their handling further downstream, we space them apart by injecting an aqueous solution at Q_{out} = 1500 µL/h, as shown in the optical micrograph in Figure 1C.[42] The resulting double emulsions have an external diameter of $D = 63 \pm 1$ µm and a shell thickness as low as $t = 0.8 \pm 0.2$ µm, as exemplified on the optical micrograph in Figure 1D and detailed in the Supporting Information.

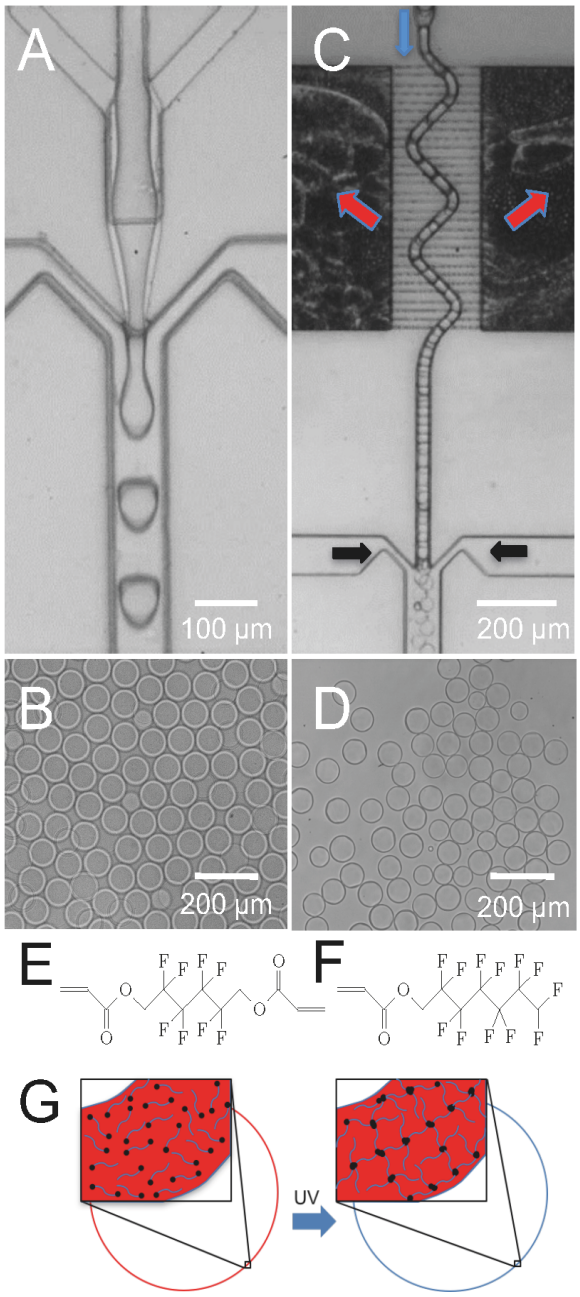

Fig. 1: (A) Optical micrograph of a microfluidic double emulsion drop maker in operation and (B) the resulting double emulsions with shell thicknesses of 9.2 ± 0.9 µm. (C) Optical micrograph of the microfluidic aspiration device in operation. The double emulsion drops flow through a S-shaped channel, and oil is removed during the process through microcapillaries, as shown with the blue arrow in the inset. Oil is evacuated through the reservoirs, as stressed by the red arrow. The black arrows show the reinjection of aqueous solution to separate the droplets. (D) Optical micrograph of the resulting double emulsions with shell thicknesses of 0.8 ± 0.2 µm. (E, F) Schematic illustration of fluorinated (E) 1H,1H,6H,6H-Perfluoro-1,6-hexyl diacrylate and (F) 1H,1H,7H-Dodecafluoroheptyl acrylate. (G) Schematic illustration of water-oil-water double emulsions before they have been exposed to UV light, where their shells contain monomers (left) and thereafter, where monomers are crosslinked to form polymeric shells (right).

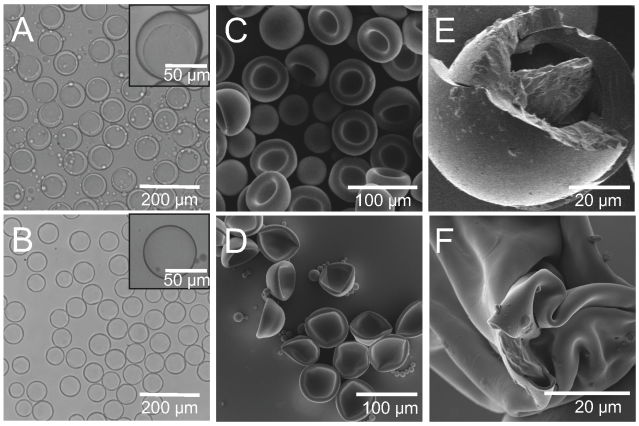

Fig. 2: (A, B) Optical microscopy images of capsules made from (A) as-produced double emulsion templates; their shells are 9.8 µm thick and (B) processed double emulsions; their shells are 0.4 µm thick. (C-F) SEM images of (C, D) intact and (E, F) cut capsules produced from (C, E) primary double emulsions with thick shells and (D, F) processed double emulsions with shin shells.

To convert double emulsions into capsules, their shells must be solidified. This can be achieved by exposing the double emulsions to UV light to initiate the polymerization reaction of the acrylates, as schematically shown in Figure 1G. The polymerized capsules are washed with deionized water before they are further characterized.

The degree of control over the mechanical properties of capsules and the release of active ingredients contained in them depends on the composition and dimensions of the capsule shells. To closely control these parameters, the thickness of the capsule shells must be uniform and well-defined. Optical micrographs of capsules made from as-produced double emulsion templates reveal large heterogeneities in the shell thickness, as shown in Figure 2A. By contrast, no significant differences in the shell thickness can be measured if capsules are produced from processed double emulsions whose shell thickness is below 1 µm, as shown in Figure 2B. However, potential heterogeneities in the dimensions of capsules with thin shells are difficult to quantify using optical microscopy because the average thickness of these shells is close to or even below the resolution limit of standard optical microscopes. To visualize the capsules with a higher resolution, we image dried capsules with SEM. Because of gravity, intact capsules will preferentially align with the thickest part of their shell facing the substrate such that the homogeneity of the shell thickness is difficult to assess from SEM images of intact capsules, as shown in Figures 2C and 2D. To assess the homogeneity of the shell thickness, we cut dried capsules with a razor blade and image them using SEM. Capsules produced from as-fabricated double emulsions have a shell thickness that varies over a wide range with the thickest part being at least 14 µm and the thinnest part being smaller than 3 µm, as seen in Figure 2E. By contrast, capsules made from processed double emulsions have uniform shells that are as thin as 400 nm, as shown in Figure 2F. These results indicate that in processed double emulsions, gravitational forces are outweighed by lubrication forces such that the center of the innermost aqueous core of the double emulsion templates is close to that of the outer, perfluorinated core.[29,34,36]

Mechanical stability of capsules

The rigidity and mechanical stability of capsules typically increases with increasing shell thickness.[46] Hence, we expect the rigidity of capsules produced from double emulsions with thick shells to be significantly higher than that of capsules produced from double emulsions with 14 times thinner shells. To test this expectation, we mechanically deform capsules by placing them between two glass slides and applying weight on the top glass slide. The capsules remain intact if they are loaded with 700 g and gradually start breaking if the load is increased until all capsules break if subjected to a load of 4 kg, as seen in Figures 3A and 3B. Remarkably, the fraction of capsules with thick heterogeneous shells that ruptures at a defined load is very similar to that of capsules with thin homogeneous shells, as seen in Figure S1. These results suggest that the thinnest parts of capsules with heterogeneous shell thicknesses have similar dimensions to those of capsules with thin homogeneous shells and that these thin parts determine the yield strength of these capsules.

To determine the mechanical properties of the capsules more quantitatively, we subject them to osmotic pressure differences. The osmolarity of the capsule core is kept constant at 0.2 Osmol/L. We vary the osmolarity of the outermost aqueous phase by changing the concentration of

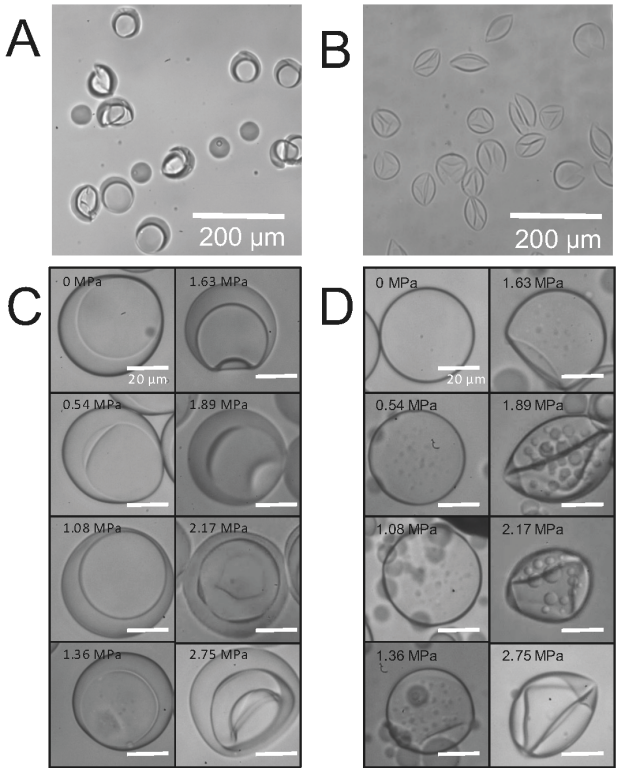

Fig. 3: (A, B) Optical microscopy images of capsules with (A) thick and (B) thin shells after having been compressed using a load of 4 kg. (C, D) Optical microscopy images of capsules with (C) thick and (D) thin shells if subjected to osmotic pressure differences ranging from 0 to 2.75 MPa.

NaCl contained in it between 0.1 and 0.66 M, corresponding to osmolarities ranging from 0.2 to 1.22 Osmol/L. As a result of the difference in the osmolarities of the two aqueous solutions, the capsules are subjected to osmotic pressures ranging from 0 to 2.75 MPa, as detailed in the Supporting Information. To assess the mechanical stability of the capsules, we incubate them under these conditions for 3 h at room temperature and quantify the percentage of intact capsules using optical microscopy. Capsules with heterogeneous, thick shells start to buckle if subjected to a pressure of 1.36 MPa. Interestingly, capsules with homogeneous thin shells start buckling at the same pressure, as shown in Figures 3C and 3D. The fact that these capsules buckle if subjected to an osmotic pressure indicates that they are permeable towards water but impermeable towards NaCl.

The pressure treshold where capsules start buckling is linearly related to the Youngs modulus of the capsule shell:[29]

$$E = \frac{\pi^* \sqrt{3(1-\nu^2)}}{2} \left(\frac{R_0}{h_0}\right)^2$$

Here E is the young modulus, π^* the pressure where buckling starts, $\upsilon = {}^1/_3$ the Poisson ratio, h_0 the shell thickness, and R_0 the external radius of the capsule. Using the measured threshold buckling pressure, π^*= 1.36 MPa, we obtain a Young modulus of $E \approx 1700$ MPa. This value is significantly higher than that of shells composed of trimethylolpropane triacrylate (ETPTA) whose Young modulus is around 600 MPa, indicating that our capsules are stiffer.[29]

Both types of perfluorinated capsules tested here remain intact even if osmotically stressed with pressures up to 2.75 MPa. These results indicate that the thinnest parts the heterogeneous shells must be almost as thin as shells of capsules produced from processed double emulsions, whose shell is 400 nm, supporting our qualitative loading results. Nevertheless, there is one important difference in the buckling behavior between capsules with thick heterogeneous and thin homogeneous shells: Capsules with heterogeneous shell thicknesses buckle at one single location only because they have one part of their shell that is very thin, as shown in Figure 3A. By contrast, capsules with homogeneous shells buckle at multiple locations such that their projected area becomes significantly smaller than that of capsules with thicker shells, as shown in Figure 3B. These results indicate that a reduction in the shell thickness of the capsules does not negatively impact their mechanical properties.

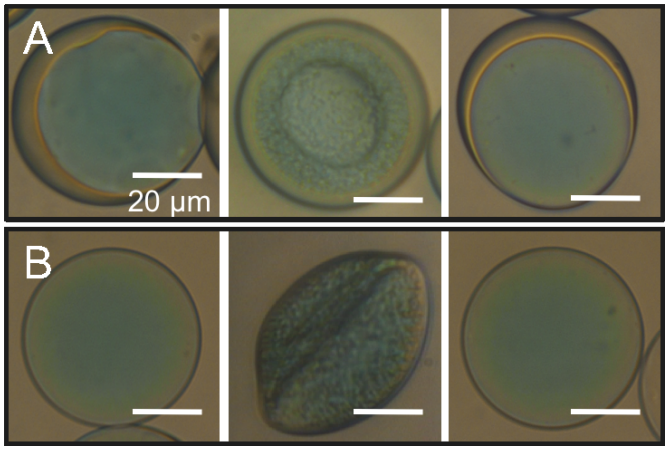

Fig. 5: Optical microscopy images of capsules with (A) heterogeneous and (B) homogeneous shell thicknesses containing a blue dye in their core. Capsules are imaged before they are dried (left), in a dry state (middle), and after being re-hydrated (right).

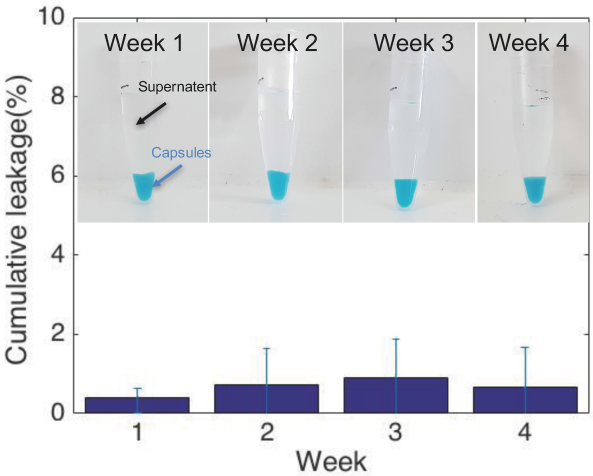

Fig. 4: Cumulative leakage of capsules with thin shells over 4 weeks measured by UV-Vis spectroscopy. Photographs of the capsules are presented in the inset. The standard deviations are calculated from four independent experiments.

Permeability of capsules

The permeability of capsules often scales with their shell thickness because this parameter determines the distance encapsulants must diffuse to cross the shell.[19,20] To test the permeability of our capsules, we load them with 2% of Patent Blue V, a dye with a molecular weight of 562 Da, and disperse them at 6 vol% in a dye-free aqueous solution. To quantify the release of encapsulants, we monitor the absorbance of the supernatent as a function of the incubation time, as detailed in the Supporting Information. Even though the shells of capsules are as thin as 400 nm, more than 98% of the encapsulants are retained over 4 weeks, as demonstrated by the small increase of the absorbance of the supernatant, shown in Figure 4. This permeability is much smaller than that measured for hydrocarbon-based capsules, whose shells are composed of crosslinked ETPTA, where the vast majority of encapsulants with similar molecular weights are released within 7 days.[27] To test the permeability of capsules towards lower molecular weight substances, we incubate empty capsules in an aqueous solution containing fluorescein, whose molecular weight is as low as 333 Da for 4 days. Capsules are subsequently washed with a fluorophore-free solution. Fluorescent microscopy images do not reveal any fluorescence inside capsules, indicating that no significant amounts of fluorescein diffuses into the capsules within 4 days, as shown in Figure S3. These results suggest that our capsules display a very low permeability even towards small molecules. Hence, our capsules can store reactive agents for a prolonged time even if

their shell is thin and release them on demand if exposed to appropriate mechanical stimuli.

It is often advantageous to store and transport capsules in a dried state because they can be stored at higher densities and the samples are lighter. These advantages can only be leveraged if capsules remain intact during drying and re-hydration cycles such that their permeability does not change. To test if our capsules fulfil these requirements, we dry capsules containing 2 wt% Patent Blue V at 70°C overnight to ensure that all the water is removed. When capsules are re-dispersed in deionized water, they inflate and attain a spherical shape within 1 hour, indicating that water diffuses through the membrane into the cores, as shown in Figures 5A and 5B. This drying and re-hydration cycle can be repeated at least three times without compromising the integrity of capsules. Importantly, their permeability towards the dye does not measurably increase upon drying and re-hydration: The dye intensity of the cores of capsules before and after they have been dried and re-hydrated is within experimental error the same, even if their shells are as thin as 400 nm, as shown in Figure 5. These results demonstrate that despite of the thin shells and hence, the low footprint, our capsules display a similar mechanical stability and permeability as capsules with much thicker shells. This opens up new possibilities to store capsules containing high concentrations of reagents in a dried state and at high densities and only re-hydrate them before usage.

Conclusion

We report the production of microcapsules with well-defined sizes and uniform shells using water-oil-water double emulsions with sub-µm thick shells as templates. The shells of these capsules are as thin as 400 nm such that the dry shell occupies only 2 % of the total capsule volume. Despite of their thin shells, the capsules are mechanically robust such that they withstand pressures of at least 1.08 MPa without being deformed and pressures up to 2.75 MPa without losing their integrity. Moreover, these semi-permeable capsules can be dried and re-dispersed at will. Because the shell is composed of a perfluorinated polymer, the capsules display a low permeability also towards small encapsulants such as Patent Blue V even though their shells are very thin; they retain more than 98% of encapsulants over 30 days. These capsules open up new possibilities to prolong the lifetime of encapsulants because they can be stored in a dried state under an inert atmosphere. Moreover, the small footprint of these capsules combined with the high mechanical stability of their shells enables their use in materials with at least one dimension that is small, such as coatings. This might enable the conversion of two component coatings into a single component or a much more efficient functionalization of materials with appropriate reagents to impart self-healing properties to them.

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Notes and references

1 D. C. Bibby, N. M. Davies and I. G. Tucker, *Int. J. Pharm.*, 2000, **197**, 1–11.
2 C. E. Mora-Huertas, H. Fessi and A. Elaissari, *Int. J. Pharm.*, 2010, **385**, 113–142.
3 A. Downham and P. Collins, *Int. J. Food Sci. Technol.*, 2000, **35**, 5–22.
4 L. Chen, G. E. Remondetto and M. Subirade, *Trends Food Sci. Technol.*, 2006, **17**, 272–283.
5 H. Hatcher, R. Planalp, J. Cho, F. M. Torti and S. V. Torti, *Cell. Mol. Life Sci.*, 2008, **65**, 1631–1652.
6 K. Miyazawa, I. Yajima, I. Kaneda and T. Yanaki, *J. Cosmet. Sci.*, 2000, **51**, 239–252.
7 M. Jacquemond, N. Jeckelmann, L. Ouali and O. P. Haefliger, *J. ofAppliedPolymer Sci.*, 2009, **114**, 3074–3080.
8 J. C. Mcdonald, D. C. Duffy, J. R. Anderson and D. T. Chiu, *Electrophoresis*, 2000, **21**, 27–40.
9 C. J. McDonald and M. J. Devon, *Adv. Colloid Interface Sci.*, 2002, **99**, 181–213.
10 G. H. Ma, Z. G. Su, S. Omi, D. Sundberg and J. Stubbs, *J. Colloid Interface Sci.*, 2003, **266**, 282–294.
11 D. E. Gorla, R. V. Ortiz and S. S. Catalá, *Parasit. Vectors*, 2015, **8**, 255.
12 E. Amstad, *Chim. Int. J. Chem.*, 2017, **71**, 334–341.
13 Y. Wang, H. Ye, C. Zhou, F. Lv, X. Bie and Z. Lu, *Eur. Food Res. Technol.*, 2012, **234**, 157–163.
14 K. F. Xiao, Z. Wang, L. L. Wang, B. H. Zhang and X. G. Feng, *Adv. Mater. Res.*, 2013, **641–642**, 939–942.
15 J.-H. Kang and E. Reichmanis, *Angew. Chemie*, 2012, **124**, 12011–12014.
16 R. Yang, Y. Zhang, X. Wang, Y. Zhang and Q. Zhang, *Sol. Energy Mater. Sol. Cells*, 2009, **93**, 1817–1822.
17 B. Shirmardi Shaghasemi, M. M. Virk and E. Reimhult, *Sci. Rep.*, 2017, **7**, 1–10.
18 E. Reimhult, *N. Biotechnol.*, 2015, **32**, 665–672.
19 L. Canaple, A. Rehor and D. Hunkeler, *J. Biomater. Sci. Polym. Ed.*, 2002, **13**, 783–796.
20 H. N. Yow, X. Wu, A. F. Routh and R. H. Guy, *Eur. J. Pharm. Biopharm.*, 2009, **72**, 62–68.
21 S. S. Datta, A. Abbaspourrad, E. Amstad, J. Fan, S. H. Kim, M. Romanowsky, H. C. Shum, B. Sun, A. S. Utada, M. Windbergs, S. Zhou and D. a. Weitz, *Adv. Mater.*, 2014, **26**, 2205–2218.
22 B. Kim, S. Lee and S.-H. Kim, *Adv. Mater. Interfaces*, 2018, **1701472**, 1701472.
23 A. Abbaspourrad, S. S. Datta and D. A. Weitz, *Langmuir*, 2013, **29**, 12697–12702.
24 A. S. Utada, E. Lorenceau, D. R. Link, P. D. Kaplan, H. A. Stone and D. A. Weitz, *Science (80-.).*, 2005, 537–541.

25 D. F. Do Nascimento, J. A. Avendaño, A. Mehl, M. J. B. Moura, M. S. Carvalho and W. J. Duncanson, *Sci. Rep.*, 2017, **7**, 1–7.
26 M. A. Zieringer, N. J. Carroll, A. Abbaspourrad, S. A. Koehler and D. A. Weitz, *Small*, 2015, **11**, 2903–2909.
27 N. Vilanova, C. Rodríguez-Abreu, A. Fernández-Nieves and C. Solans, *ACS Appl. Mater. Interfaces*, 2013, **5**, 5247–5252.
28 B. J. Sun, H. C. Shum, C. Holtze and D. A. Weitz, *ACS Appl. Mater. Interfaces*, 2010, **2**, 3411–3416.
29 S. S. Datta, S. H. Kim, J. Paulose, A. Abbaspourrad, D. R. Nelson and D. A. Weitz, *Phys. Rev. Lett.*, 2012, **109**, 1–5.
30 M. . Krafft and J. . Riess, *Biochimie*, 1998, **80**, 489–514.
31 J. G. Riess and M. P. Krafft, *MRS Bull.*, 1999, **24**, 42–48.
32 W. R. Jones, T. R. Bierschenk, T. J. Juhlke, H. Kawa and R. J. Lagow, *Ind. Eng. Chem. Res.*, 1988, **27**, 1497–1502.
33 A. Vitale, M. Quaglio, M. Cocuzza, C. F. Pirri and R. Bongiovanni, *Eur. Polym. J.*, 2012, **48**, 1118–1126.
34 C. X. Zhao, D. Chen, Y. Hui, D. A. Weitz and A. P. J. Middelberg, *ChemPhysChem*, 2017, **18**, 1393–1399.
35 C. Zhao, D. Chen, Y. Hui, D. A. Weitz and A. P. J. Middelberg, 2016, **02138**, 1553–1556.
36 S.-H. Kim, J. W. Kim, J.-C. Cho and D. a Weitz, *Lab Chip*, 2011, **11**, 3162–3166.
37 H. C. Shum, D. Lee, I. Yoon, T. Kodger and D. A. Weitz, 2008, **24**, 7651–7653.
38 H. C. Shum, J.-W. Kim and D. a Weitz, *J. Am. Chem. Soc.*, 2008, **130**, 9543–9.
39 S. H. Kim, J. W. Kim, D. H. Kim, S. H. Han and D. A. Weitz, *Microfluid. Nanofluidics*, 2013, **14**, 509–514.
40 S.-H. Kim, J. Nam, J. W. Kim, D.-H. Kim, S.-H. Han and D. A. Weitz, *Lab Chip*, 2013, **13**, 1351.
41 A. Vian, V. Favrod and E. Amstad, *Microfluid. Nanofluidics*, 2016, **20**, 1–9.
42 A. Vian, B. Reuse and E. Amstad, *Lab Chip*, 2018, **18**, 1936–1942.
43 Y. N. Xia and G. M. Whitesides, *Annu. Rev. Mater. Sci.*, 1998, **37**, 551–575.
44 G. M. Whitesides, *Nature*, 2006, **442**, 368–373.
45 L. R. Arriaga, E. Amstad and D. a. Weitz, *Lab Chip*, 2015, **15**, 3335–3340.
46 A. Fery and R. Weinkamer, *Polymer (Guildf).*, 2007, **48**, 7221–7235.