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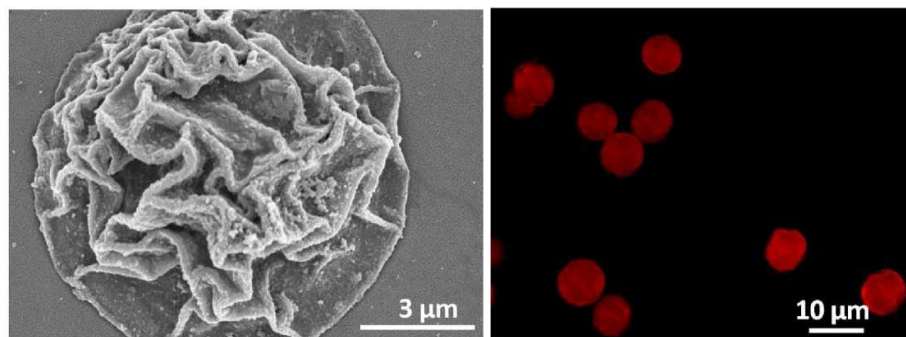
ARTICLE TYPE

Preparation of Elastic Polyurethane Microcapsules using CaCO₃ Microparticles as Templates for Hydrophobic substances loading

Xiaofan Liu, Shupeng She, Weijun Tong*, Changyou Gao

Elastic polyurethane (PU) microcapsules were successfully fabricated via a simple and well controllable adsorption and crosslinking method on porous CaCO₃ templates in organic solvent. The PU capsules possessed some amine groups, enabling well dispersion in water. These PU capsules with hydrophobic interiors could load hydrophobic substances such as drugs and dyes from organic solution spontaneously.
10 And the loaded dyes can be well preserved. Their deformation and recovery behaviours were investigated after being forced to flow through a microchannel. Due to their good elasticity, more than 82% squeezed PU capsules could recover their original spherical shape even at a high deformation ratio of 32%. These elastic PU microcapsules with strong shape recovery ability may find diverse applications as microcontainer or microsensor which could survive through harsh conditions like forced deformation.

15

Introduction

The microcapsules have opened up fascinating avenues to a broad range of biomedical applications[1] such as drug delivery,[2, 3] biosensors,[4] bioreactors,[5] catalysis and biomimetic fields[6]
20 because of their tailored structures and integrated functionalities. On one hand, most of the capsules or particles have been used to encapsulate hydrophilic substances like proteins. On the other hand, the ability to load poorly water soluble materials (like most drugs) is also very important, because above 40% new
25 pharmacologically active compounds identified through screening of combinatorial libraries are poorly water-soluble.[7] More importantly, the diameter of microcapsules (about several micrometers) is relatively big compared with the size of blood capillary (~3 μm for the smallest) in the body, leading to a barrier
30 to their potential applications in vivo. Although some attempts have been made to solve the problem via the red blood cell-like microparticles,[8, 9] hydrogels[10] and polyelectrolyte multiplayer microcapsules[11] with different sizes and shapes possessing good deformation and recovery ability under flow condition, the
35 microcapsules with better elasticity and thereby shape-persistency are much attractive to challenge this barrier, and are deserved extensive investigation.

Polyurethane (PU) is widely used in biomaterials and shape memory fields due to their good elasticity and highly flexible
40 chains resulting from their specific micro-phase structure, blood compatibility with strong anticoagulant activity, and its ability to be engineered to have a wide range of mechanical properties through the selection of various soft and hard segments.[12-16] PU materials can be used in the forms of micelles, nanoparticles,
45 scaffolds, capsules and so on. Among them, PU microcapsules

have been used to encapsulate diverse substances including pesticides, corrosion inhibitor,[17] drugs and proteins,[18] various dyes[19] and especially oils and organic solvents.[20] They can be used in painting and coating,[21] self-healing materials,[22] heat
50 transfer and medical fields. So far the fabrication of PU capsules has been focused on interfacial polymerization,[23, 24] emulsion and diffusion methods[22] and micelles,[25] which are hard to precisely control over the size, shape, morphology and inner structure of capsules.
55 In the various methods[26] for fabricating microcapsules, the template synthesis on a sacrificial core[27] has attracted considerable attention because of their high surface areas, unique pore structures and tunable particle morphology. It has been widely used to fabricate multifunctional microcapsules and other
60 micro-structured materials. Recently, porous CaCO₃ microparticles became the attractive templates due to their simple preparation procedure, biocompatibility, cost-effectiveness and mild removal conditions.[28] For example, by layer-by-layer assembly of oppositely charged polyelectrolytes onto porous
65 CaCO₃ templates, followed by removal of CaCO₃, matrix polyelectrolyte microcapsules have been prepared.[29] The inner structure of the porous CaCO₃ templates could be tuned by changing synthesis conditions, resulting the cell-like multilayer microcapsules.[30] By polymerizing the infiltrated molecules in the
70 porous template, porous microcapsules or microspheres could be fabricated after template removal.[31] Yan et al[32] loaded poly-L-lysine(PLL) modified nanoparticles into porous CaCO₃ microspheres and followed by crosslinking with glutaraldehyde (GA) or dimethyl pimelimidate dihydrochloride (DMP), and
75 obtained hybrid colloidal spheres integrating the functionalities of bioorganic components and inorganic nano-objects after template
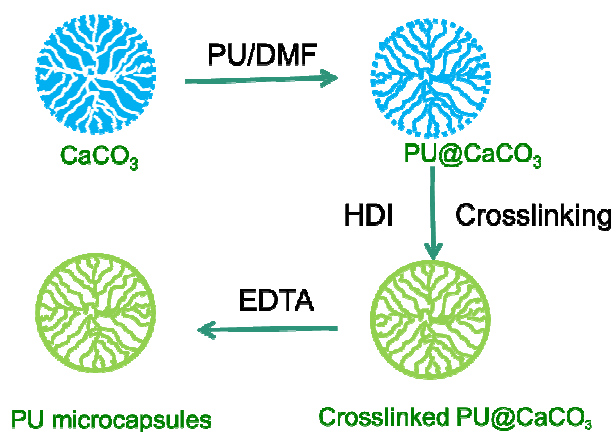
Figure 1. Schematic illustration of the fabrication process of PU microcapsules.

removal.

Herein, we integrate the elasticity of PU material and the simple and well controllable adsorption and crosslinking method on porous $CaCO_3$ templates[33] for the construction of elastic PU microcapsules, and further study their capability for loading of hydrophobic substances and their deformation and recovery property after squeezed through a self-made microchannel with a height smaller than the capsules' diameter. This approach involves infiltration of PU into the nanopores of the $CaCO_3$ particles in organic solvent, cross-linking of the polymer chains, and removal of the $CaCO_3$ particle templates (Fig. 1). Compared with previous studies, fabrication of capsules in organic solvents greatly expands the range of materials adopted by this technique. More importantly, the new materials such as PU here can endow the capsules with new properties and functions such as the elasticity. The ability of loading of low-molecular-weight hydrophobic dyes into the capsules is also demonstrated. The deformation and recovery behaviors of this kind capsules passing through a microchannel are observed on line by confocal laser scanning microscopy (CLSM). This property can help the microcapsules to pass through the blood capillary vessel when they are used in vivo in the future.

Experimental section

Materials:

Polyurethane (PU, Mn~58 kDa. The shore hardness is 65A, implying elastic) was obtained from Yantai Wanhua Polyurethane Co., Ltd. China. Hexamethylene diisocyanate (HDI) and stannous octoate were obtained from Acros. Coumarin 6 was obtained from Sigma-Aldrich. Dimethyl formamide (DMF), toluene, $Ca(NO_3)_2 \cdot 4H_2O$ and Na_2CO_3 were obtained from Sinopharm Chemical Reagent Co., Ltd. Ethylenediaminetetraacetic acid disodium salt (EDTA) was purchased from Guangdong Guanghua Chemical Factory Co., Ltd. All chemicals were used as received. The water used in all experiments was prepared in a Millipore Milli-Q Reference purification system.

Preparation of $CaCO_3$ microparticles[11]:

100 mL 0.33 M Na_2CO_3 solution was added to an equal volume of 0.33 M $Ca(NO_3)_2$ solution under mechanical agitation (900 rpm) for 1 min at room temperature. After 20 min, the suspension was centrifuged (2000 rpm, 1 min) and washed with ethanol 3 times, and then the particles were dispersed in ethanol for later use.

Preparation of PU microcapsules:

PU was first dissolved in DMF with a concentration of 10 wt%. The porous $CaCO_3$ particles (0.5 g) were incubated in 10 mL PU solution for certain time to load the PU into the inner pores of $CaCO_3$ spontaneously. Then the particles were washed by DMF and ethanol 3 times by centrifugation and dried at 70 °C in an oven for 5 h. The obtained PU-loaded $CaCO_3$ particles (1 g) were dispersed in HDI solution (25 mg in 10 mL toluene with 5 mg stannous octoate as catalyst) for 1 h to crosslink the adsorbed PU. After washed by ethanol 3 times and separation by centrifugation (2000 rpm, 1 min), the particles were incubated in 0.2M EDTA for 2 h to ensure the complete $CaCO_3$ removal. The obtained microcapsules were washed by water 3 times and separation by centrifugation (5500 rpm, 10 min) and dispersed in water.

The loading and release of coumarin 6:

To load coumarin 6 into the capsules, 0.5 mL microcapsule suspension (~6×10^6/mL in water) was mixed with 1 mL coumarin 6 solution (1 mg/mL in ethyl acetate), and the mixed solution was shaken overnight. After centrifugation (6000 rpm, 10 min) and discard of supernatant, the microcapsules were washed with water 3 times and finally dispersed in water. 1 mL suspension of the dye-loaded capsules was centrifugated, and the supernatant was discarded. The capsules were re-incubated in 1 mL ethyl acetate for 0.5 h under shaking to extract coumarin 6. After centrifugation (5500 rpm, 10 min), the concentration of coumarin 6 in the supernatant was determined with a UV-vis spectrophotometer (UV-2550, Shimadazu, Japan) at 442 nm by referring to a calibration curve. Each value was averaged from three parallel measurements.

The release of coumarin 6 from PU microcapsules was studied at 37 °C in PBS (pH=7.4). In a typical experiment, 1ml dye-loaded capsules (~3×10^8/mL in PBS, pH=7.4) was transferred to a dialysis bag with a cut off Mw of 8-14 kDa, which was immersed in 10 mL of pH 7.4 PBS at 37 °C. Then 1 mL incubation medium was taken out for UV-vis measurement and 1 mL fresh PBS of the same pH was supplemented at desired time intervals. The results were averaged from triplicate experiments.

The microchannel experiment:

The microchannel was fabricated via the photolithographic and wet chemical etching methods as described previously.[11] Access holes were drilled with a 1.2 mm diameter diamond-tipped drill bit at each terminal of the groove, and followed by permanently covered with a thin cover slip through a thermal bonding procedure and glued to a pipet tip head at each terminal on the back side of the glass slide. Thus, the microchannel with a height of 4.7 μm in Z direction and a function of the sample supply and collection was successfully fabricated. The suspension of microcapsules in water was diluted sufficiently to avoid clogging of capillary and the collision among capsules. 50 μL of the diluted suspension of microcapsules was added to the access hole at the inlet, with the same amount of water in the two sheath fluid

inlets. A negative pressure (0.77 atmosphere pressure) was applied at the outlet to force the movement of microcapsules in the microchannel. All the capsules passed through were collected in the small cell at the outlet and used for subsequent
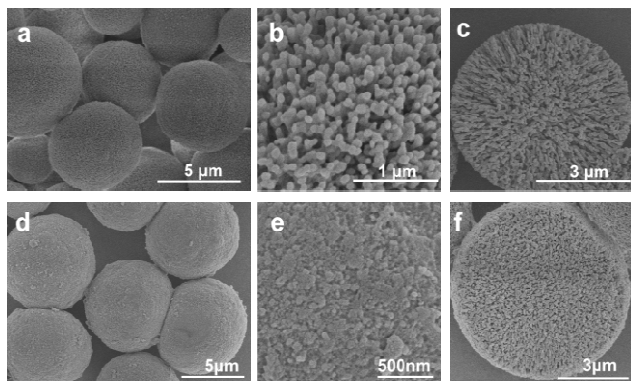
5 Figure 2. SEM images of (a) $CaCO_3$ microparticles, and (b) their surface and (c) cross section morphology, and (d) crosslinked $PU@CaCO_3$ microparticles, and (e) their surface and (f) cross section morphology.

characterizations. During the experiment, the capsule could be trapped within the microchannel by releasing the negative
10 pressure for in situ observation.

Characterizations

Scanning electron microscopy (SEM):
A drop of $CaCO_3$ particles or microcapsules suspension was placed on a clean glass slide and dried at ambient temperature
15 overnight. The samples were sputtered with gold, and then observed with HITACHI S-4800 instrument at an operation voltage of 3 kV. Energy dispersive X-ray spectroscopy (EDX) analysis was carried out on a Phoenix EDAX, GENEMS 4000, attached to a scanning electron microscope for 200 s.
20 **Confocal laser scanning microscopy (CLSM):**
Confocal images were taken with a Leica TCS SP5 confocal scanning system equipped with a ×100 oil immersion objective. At least 200 capsules were analyzed by Image J software in order to determine the capsule diameter. The microcapsules trapped in
25 the microchannel and those passed through were also characterized by CLSM in a Z series mode, and a series of images were reconstructed by Leica software to show their 3D topographies.
Transmission electron microscopy (TEM):
30 The PU capsules were washed with water thrice and then with graded ethanol/water mixed solutions. The sample was embedded into epoxy resin and ultramicrotomed into thin sections, which were transferred onto a carbon film-coated copper grid and observed by a Philips Tecnal-10 TEM.
35 **Fourier transform infrared spectroscopy (FTIR):**
FTIR was measured on a Vector 22 spectrophotometer (Bruker optics, Switzerland) using a thin film on a KBr substrate for PU materials or KBr pellet for PU microcapsules. The samples were completely dried in oven before measurement.
40 **Fluorescence spectroscopy:**
The microcapsules in water (0.8 mL, ~1.5×10^6/mL) was mixed with Nile red in ethyl acetate solution (0.8 mL, 1 mg/mL) for 24 h, followed by centrifugation and washed with water, and finally dispersed in water. The emission in the range of 600–750 nm
45 (excited at 488 nm) was collected using a FL-55 fluorometer

(Perkin Elmer, Japan).
Bunauer-Emett-Tller (BET):
The pure $CaCO_3$ particles, two kinds of $CaCO_3$/PU particles (fabricated by incubation in 10% PU solution for 20 min and 24
50 h, and followed by 20 min HDI crosslinking, respectively) were outgassed at 75 °C in a vacuum oven for 24 h. After being absolutely dried and outgassed, the N_2 adsorption–desorption isotherms were recorded on the BET measurement apparatus (TriStar II 3020) using nitrogen as adsorbate at -196 °C. The
55 surface area value was analyzed in the Barrett–Joyner–Halenda (BJH) method by a computer program.
Zeta Potential:
The ζ-potential of microcapsules in water was measured by a Delsa Nano C particle size and ζ-potential analyzer (Beckman
60 Coulter). The value was averaged from 3 parallel measurements.

Results and discussion

Preparation of microcapsules with specific size, morphology and structure on $CaCO_3$ templates has received much attention.[29, 34, 35] Via a simple adsorption and crosslinking method, microcapsules
65 can be fabricated after template removal, as shown in this work. The $CaCO_3$ particles had a spherical shape and an average size of 7.2±0.4 µm (Fig. 2a) with porous surface (Fig. 2b) and fiber-like inner structure (Fig. 2c). The average pore size was 70.8 nm, which is comparable with previous report.[29] After PU adsorption
70 and crosslinking, the pores of the template were blocked and the particle surface became smoother (Fig. 2d-e). The cross section of PU-adsorbed particle (Fig.2f) shows that a new layer was likely formed on the particle surface by comparison with Fig. 2c. The average pore size decreased to 21.3 nm, indicating the
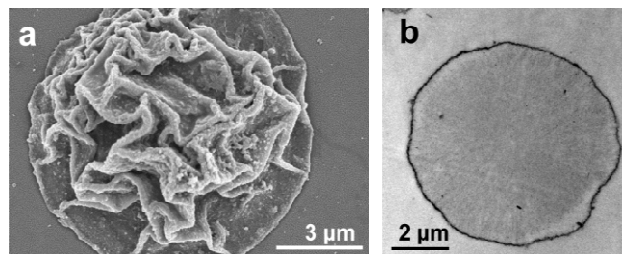75 successful loading of PU into the pores of templates.[32]

Figure 3. (a) SEM image, (b) TEM image of a PU microcapsule fabricated by incubation in 10% PU solution for 24 h followed by 1 h HDI crosslinking.

80 After template removal, the PU microcapsules were obtained. SEM images (Fig.3a) reveal that the capsules collapsed with a non-flat morphology and considerably high folds in the middle parts of the capsules, which is substantially different from that of capsules templated on colloids of smoother surface texture.[9] This
85 special morphology is most possibly induced by matrix inside the capsules or the thicker shells,[29, 36] which may prevent the full collapse of the shells. The template of $CaCO_3$ is porous and the PU can be easily adsorbed into the pores, leading to an matrix microcapsule.[29] TEM image (Fig. 3b) indicates that there are
90 some substances inside of the microcapsules, forming a network structure from the center to the periphery.[37] This is consistent with the adsorption of PU inside the porous $CaCO_3$ particles, which is then fixed in situ by HDI. Such a structure is the inverse replica of the $CaCO_3$ template. Energy dispersive X-Ray

spectroscopy (EDX) results showed that there was only trace amount of Ca (0.01% by Atom) in the microcapsules, meaning the template was removed (Fig. S1). Some other methods such as interfacial polymerization can also prepare PU capsules, whose
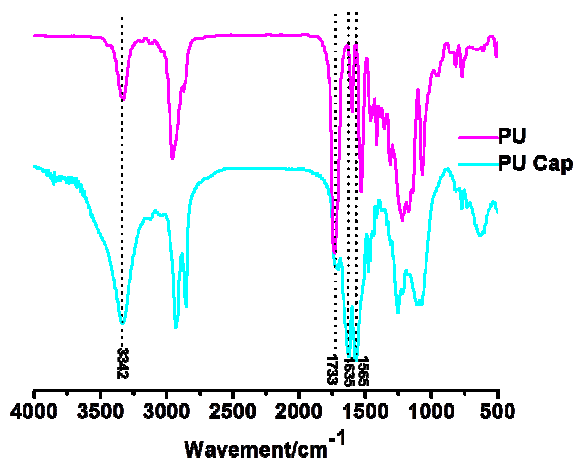5 size is always in the order of dozens of micrometers[21, 23] or even

Figure 4. FTIR spectra of PU raw material (PU) and PU microcapsules (PU Cap, fabricated by incubation in 10% PU solution for 24 h followed by 1 h HDI crosslinking).
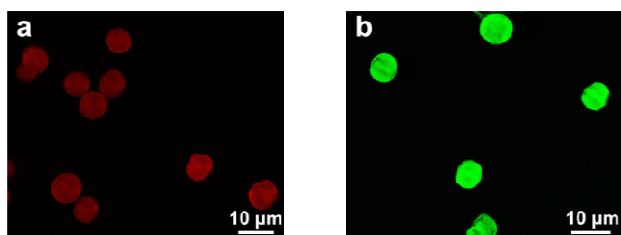

Figure 5. CLSM images of PU microcapsules loaded with hydrophobic
10 dyes of (a) Nile red and (b) coumarin 6.

bigger.[24] Smaller capsules even in the order of nanometers can be prepared by a mini-emulsion method.[18] However, the common problems of these methods are the large distribution of the capsule size, and hard control over the surface morphology, not
15 even to say the inner structure. The present method can easily control the PU capsule size by the template, and even adjust the inner and surface morphology as shown by the above results.

The resulted microcapsules could be well dispersed in water with a diameter of about 7.2 μm, almost same to that of the template.
20 The surface zeta potential of the microcapsules was +17.1 mV. The well dispersity and the positive surface charge can be attributed to the amino groups on the microcapsules due to the hydrolysis of unreacted isocynate groups in HDI,[38] which is revealed by FTIR characterization. Compared with that of the PU
25 raw material, the absorbance peaks (3342, 1635 and 1565 cm^{-1}) of amine or amide[39] in the PU microcapsules (PU Cap) were enhanced significantly (Fig. 4). By contrast, the ester vibration at 1733cm^{-1} was weakened apparently.

Although the PU capsules possess some amine groups which
30 facilitate the dispersion of the microcapsules, the major matrix of PU materials is intrinsically hydrophobic and water-insoluble. This feature enables the loading of hydrophobic substances such

as coumarin 6 and Nile red (Fig. 5). The fluorescence spectra of Nile red can be used to monitor the domain environment of the
35 microcapsules, as this dye is solvatochromic, and the position of the peak implies the hydrophobicity of the domain environment where Nile red exists.[40] The peak in microcapsules of 620 nm
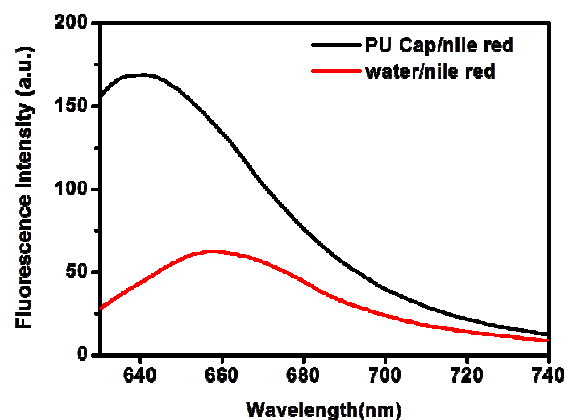

Figure 6. Fluorescence emission spectra of PU microcapsules loaded with Nile red, and Nile red in water.

40 was blue-shifted compared with that in water at 660 nm (Fig. 6), indicating the hydrophobic domain environment in the microcapsules.[40] Such a hydrophobic environment is very important for the encapsulation of hydrophobic substances. Different from other types of microcapsules, the as-prepared PU
45 microcapsules can be well dispersed in water, but possess the ability to suck hydrophobic substances from organic solution.

The influences of the experimental parameters such as the concentrations of PU(1%, 2%, 6% and 10%), the adsorption time of PU (20min, 2h and 24h), and crosslinking time (20min, 1h, 3h)
50 on the obtained PU microcapsules have been studied. The lower concentration of PU, shorter adsorption time of PU and cross-linking time resulted thinner capsules with fewer folds, indicating less PU was adsorbed and crosslinked, and the microcapsules became less intact. (Data not shown) When the crosslinking time
55 was longer than 20 min and the concentration of PU was above 2%, they would not obviously influence on the structure of the obtained capsules. However, at the fixed PU concentration of 10% and crosslinking time of 1 h, the adsorption time had significant impact on the resulted microcapsules. When the
60 adsorption time increased form 20 min to 24 h, the surface area of PU@CaCO$_3$ decreased from 10.1 m^2/g to 7.1 m^2/g, suggesting more PU was deposited into the template. After template removal, the shell became thicker and the number of typical folds and creases increased (Fig. S2), meaning a typical sign of mass
65 increase in the capsules. The larger mass in the capsules enhanced the loading amount of hydrophobic substances as well. For example, the loading amount of coumarin 6 in one capsule fabricated via 20 min PU adsorption was 3.4±0.4 pg. When the adsorption time increased to 24h, this value also increased greatly
70 to 15.0±0.5 pg (Fig. S3). The release of coumarin 6 was negligible in PBS at 37 °C for even 48h, and no peak value was detected by the UV-vis. This is due to the negligible solubility of coumarin 6 in water and it prefers to stay in the relatively

hydrophobic interior of capsules (Fig. 6). This result reveals that the capsules can suck hydrophobic substances from organic solution and the hydrophobic dye molecules are well preserved inside the capsules.
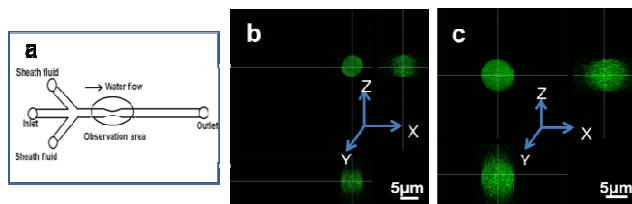

5   Figure 7. (a) Scheme of the microchannel. Series Z-scanning CLSM images of a microcapsule (b) within the microchannel and (c) out of the microchannel after being squeezed through. The capsules were stained with coumarin 6.

The PU microcapsules are assumed to have a good elasticity
10 because of the elastic PU materials. To verify this assumption, the PU microcapsules with a diameter of 7.2±0.4 μm (fabricated by incubation in 2% PU solution for 20 min followed by 20 min HDI crosslinking) were forced to pass through a microchannel. By laser scanning microscopy, the key geometric features of the
15 microchannel used in this study were characterized with a depth (size in Z direction) of 4.7 μm and a width (size in Y direction) of 35 μm of the constriction region, and the length of the constriction is about 150 μm. At the both sides of the constriction region, the depth and width of the channel are about ∼25 μm and
20 75 μm, respectively. By this way, the PU microcapsules are forced to deform in Z-direction (4.7 μm) if they can pass through the microchannel (Fig. 7a). From the experiment, we find the capsules can successfully pass through the channel. If we release the negative pressure at a proper time, the capsules can be
25 stopped within the channel (Fig. S4). As evidenced by the series of Z-scanning images of the PU microcapsules captured by CLSM, obvious shape deformation in Z direction did occur when they were trapped inside the microchannel (Fig. 7b). After being squeezed from the microchannel, the deformation of the capsules
30 disappeared completely, suggesting the elastic recovery of the microcapsules (Fig. 7c, Fig. S5, 6). Statistic analysis found a recovery ratio of 82.4%, and the capsule size was identical to the original one. These results demonstrate that the capsules can recover their shape when the deformation ratio is as high as 32%
35 (The deformation ratio is defined as $(D_{cap}-D_{cns})/D_{cap}\times100\%$, where D_{cap} and D_{cns} are the capsule diameter and constriction depth, respectively). Such good elasticity may originate from both the elastic PU materials and the inner network structure of the PU microcapsules, since it is known that the substances inside
40 facilitate the shape recovery after releasing the physical constriction.[11] Previous results showed that the recovery percentage of the poly(allylamine hydrochloride) (PAH)/poly(styrene sulfate) (PSS) multiplayer microcapsules was as low as ∼15% at a similar deformation ratio.[11] Therefore, The
45 PU capsules have a much stronger ability to maintain their spherical shape subjecting deformation and force release. It is worth mentioning that the PU capsules fabricated by 10% PU, 24 h incubation and 1 h HDI crosslinking could not pass through the microchannel at the same experimental conditions. It is
50 understandable that higher force will be required to deform these stiffer PU capsules with more dense structure and higher

crosslinking degree. Therefore, the deformation and recovery property of the PU microcapsules is greatly influenced by the preparation conditions.

55 To study the release of dye from the capsules after passing through the microchannel, it is difficult to use the general used protocol for drug release studies because the collected capsules are very few. According to the reference, CLSM was used to measure the fluorescent intensity of capsules before and after
60 they passed through the microchannel, which is correlated to the content of dye inside the capsules.[41] After squeezed through the microchannel with a diameter of 4.7 μm, the coumarin 6 content inside the capsules was not changed significantly (Fig. S7), revealing that the dye molecules are stably loaded regardless of
65 the water flow and capsule deformation. This may be due to the hydrophobic property of coumarin 6. This property is important for future applications such as fluorescent micro-sensors where the dye molecules should be well preserved when the capsules are squeezed through narrow capillaries.

Conclusion

70 The elastic PU microcapsules were successfully fabricated by a simple and well controllable adsorption and crosslinking method by using porous $CaCO_3$ particles as sacrificial templates. The interior of the capsules had a network structure from the center to
75 the periphery. The PU capsules had some amine groups, enabling well dispersion in water. The matrix of PU capsules could still suck hydrophobic substances such as Nile red and coumarin 6 from organic solution. The hydrophobic dyes can be well maintained inside the capsules. 82% capsules could recover their
80 original shape after they were squeezed through a microchannel with a deformation ratio of 32%, and the low molecular-weight dyes can be stably maintained regardless of squeezing through the microchannel. These elastic PU microcapsules may find promising applications in the adsorption and removal of
85 hydrophobic molecules, microsensors with stable loaded fluorescent dyes and so on.

Acknowledgements

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Notes and references

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