Functional Particles

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Microscale Polymer Bottles Corked with a Phase-Change Material for Temperature-Controlled Release**

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Over the past few decades, considerable endeavor has been devoted to controlling the release of drugs. Most of the studies have focused on the achievement of a prolonged release by developing a wide variety of carriers.[1–4] There are, however, many situations in medical procedures that require more than a sustained, continuous release of the drug.[5] For example, studies in chronopharmacology have demonstrated that the onsets of certain diseases exhibit strong circadian temporal or physical dependence.[6] Treating such diseases requests a smart control over the release pattern of a drug, in response to either in vivo physiological status or external stimuli.[7–9] A fast response of the drug carrier to the stimuli will allow for a real-time manipulation of the dosage. The concept of stimuli-regulated release has been developed for pH value,[10] temperature,[11,12] ultrasound,[5,9] mechanical signal,[13,14] and electric,[15,16] or magnetic fields.[17,18] Among them, temperature has been widely used as a stimulus to trigger the drug release because local body temperature can vary in response to surrounding conditions and different stages of a disease.[19] To date, a handful of materials with thermosensitive properties have been investigated for temperature-regulated drug release.[20,21] However, the drug release systems fabricated from these materials have several shortcomings for use in practical applications, including, for example, 1) slow loading, 2) noticeable release at the initial point owing to free diffusion of the drug, 3) low encapsulation efficiency, and 4) insufficient amount of drug loading.[19]

Herein we demonstrate a new system for temperature-controlled release. The system consists of a polymer hollow particle with a hole on its surface. The hole allows for quick, efficient loading of small molecules, macromolecules, and even nanoparticles at least 50 nm in size. The temperature-controlled release can be realized by corking the hole with a phase-change material (PCM) capable of reversible, solid–liquid transition in response to variation in temperature.[22] Below its melting point, the PCM will be in a solid state to completely block the passing of encapsulated species. When the temperature is raised beyond its melting point, the PCM will quickly melt to release the encapsulated species.

Figure 1 a shows a schematic of the procedure used in the fabrication of polymer hollow particles with holes on their surfaces. Polystyrene (PS) beads with a uniform size were

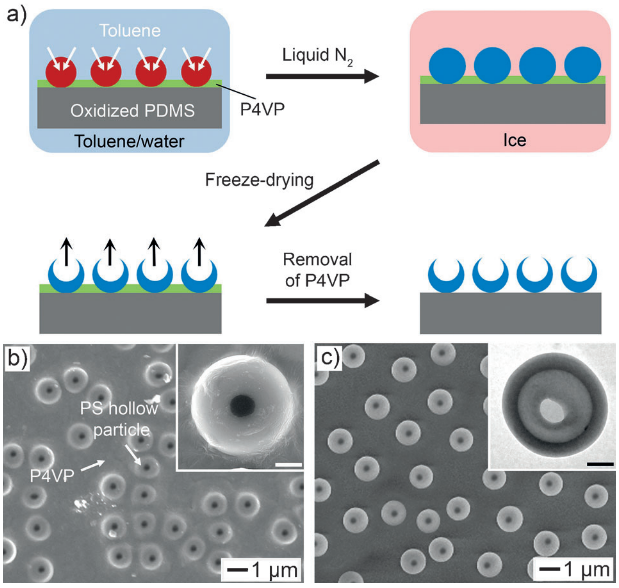

Figure 1. a) Schematic illustration of the procedure for generating polymer hollow particles carrying a small hole on the surface. It involves four major steps: diffusion of toluene into the PS beads partially embedded in a thin film of P4VP, quick freezing by liquid N_2, evaporation of toluene under freeze-drying, and removal of the P4VP film. b) SEM image showing the PS particles with a hole on the surface. Inset: magnified view of the particle to show the hole more clearly. c) SEM image showing the particles after the P4VP film had been selectively removed. Inset: TEM image indicates that the particle was still spherical and hollow. The scale bars in the insets are 300 nm.

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Supporting information for this article (Experimental details; SEM image of the rubbed PS particles; optical micrograph showing the surface of PDMS substrate after removal of hollow PS particles by ultrasonication; TEM and SEM images showing the structure change of hollow particles depending on the volumetric ratio of toluene/water; curve of the radius of inside void as a function of the mixing ratio of toluene/water (vol); and release profiles for Rhodamine B from the PS hollow particles capped by 1-tetradecanol in a buffer solution at pH 4.0.) is available on the WWW under http://dx.doi.org/10.1002/anie.201305006.

deposited on a relatively soft poly(dimethylsiloxane) (PDMS) substrate (20:1, w/w), and then rubbed with a more rigid PDMS substrate (2:1, w/w) to prevent aggregation among the beads.[23] Because the more rigid PDMS has a much lower adhesive force,[24] the mechanical rubbing could assist an even distribution of the beads without peeling them off from the soft PDMS substrate (see Figure S1 in the Supporting Information). The beads were then partially embedded in a thin film of poly(4-vinylpyridine) (P4VP) through a transfer and pressing process. The P4VP film was prepared by spin-coating a P4VP solution in ethanol on a flat PDMS substrate (40:1, w/w) that had been pre-treated with O_2 plasma (PE-50, Plasma Etch Inc.) to facilitate the wetting process. The embedded beads were then soaked in a mixture of toluene and water. The immiscibility between water and toluene forced the toluene to diffuse into the beads. In the final step, the mixture was quickly frozen in liquid nitrogen (−196 °C), followed by freeze-drying in vacuum and removal of the P4VP matrix.

Figure 1 b shows SEM image of the PS particles that were partially embedded in a film of P4VP. As shown in the inset, each particle had a hole of approximately 0.25 μm in diameter on its surface, which was a result of the evaporation flux of toluene.[25] When the frozen sample was slowly warmed up in vacuum to reach a temperature close to the melting point of toluene (−95 °C), the PS chains would move toward the surface of each particle as a result of the evaporation flux of toluene, leading to the formation of a hole. The position of the hole was consistent with the direction of evaporation. The P4VP film was then carefully removed by immersing the sample in ethanol. Figure 1 c shows SEM image of the particles after the P4VP film had been removed. Interestingly, the original positions and orientations of the particles could both be retained very well because the remaining P4VP could still hold the particles in place (Figure S2). Since the particles were swollen by toluene, their radius increased from 0.48 ± 0.01 to 0.62 ± 0.02 μm. For further characterization by TEM, the particles were released from the PDMS substrate by ultrasonication. A TEM image of the released particle demonstrates that the particle was still spherical and hollow (Figure 1 c, inset). The spherical shape could only be maintained when the thickness of P4VP film was kept less than half of the particle diameter. Otherwise, the particles would be deformed to a less symmetrical shape because too much embedding in the P4VP matrix would affect the swelling of the beads.

The structure of the particles could be varied by controlling the amount of solvent used to swell the polymer beads. Figure 2 a–c, shows SEM images of the PS particles that were obtained by swelling the beads with mixtures of toluene and water in different volume ratios. The ratio had a direct impact on the size of hole formed on the surface of a particle. The sizes of the holes were 0.05 ± 0.01, 0.35 ± 0.07, and 0.60 ± 0.08 μm, respectively, when the toluene-to-water ratio was increased from 0.01 to 0.05 and then 0.075. This change can be attributed to the difference in magnitude for the evaporation flux of toluene. Assuming the total volume of PS chains and the size of each swollen particle did not change during the whole process, the volume fraction (ϕ) of PS chains in each particle can be calculated as $\phi = (R_{PS}/R_{PS/T})^3 = (R_{PS}/R_{hollow\text{-}PS})^3$, where R_{PS}, $R_{PS/T}$, and $R_{hollow\text{-}PS}$ are the radii of pristine, swollen, and hollow PS particle, respectively. The solvent evaporation flux (J) increases with the volume fraction $(1-\phi)$ of solvent in the polymer solution and can be expressed as $J = J_0\ (1-\phi_t)$, where J_0 is a constant and ϕ_t is the volume fraction of polymer at time t.[26,27] The plots in Figure 2 d show the changes in the hole size (D_H) and volume fraction of solvent $(1-\phi)$ for the swollen particles as a function of toluene-to-water ratio. For the calculation of ϕ, we used the average values of measured $R_{hollow\text{-}PS}$: 0.55, 0.65, and 0.70 μm for the solvent ratios of 0.01, 0.05, and 0.075, respectively. Although the evaporation process involved a dynamic change to the volume fraction of solvent, the two plots show very similar behavior as a function of the solvent ratio. This result suggests that the initial flux of evaporating toluene led to the formation of hole, which then became a preferred path for the evaporation of the remaining solvent. A stronger flux would result in the formation of a bigger hole. The size of void inside the particle was also dependent on the solvent ratio (Figure S3). The radius of void (R_V) can be calculated using the following equation:[25] $R_V = [(R_{hollow\text{-}PS})^3 - (R_{PS})^3]^{1/3}$. The predictions (see Figure S4) from this equation were in good agreement with the values measured from the TEM images in Figure S3. For example, a solvent ratio of 0.01 corresponded to R_V of 0.32 μm, and a solvent ratio of 0.075 increased R_V to 0.61 μm. When the solvent ratio was increased beyond 0.1, the polymer would be highly swollen and partially dissolved so that the condensed viscous polymer phase fluctuated at the surface to form protruded structures (Figure S5a). At a higher solvent ratio, the shear force caused by the mechanical agitation selectively dissolved out the PS portion that was not embedded in the P4VP layer, resulting in a hemisphere with porous surface (Figure S5b).

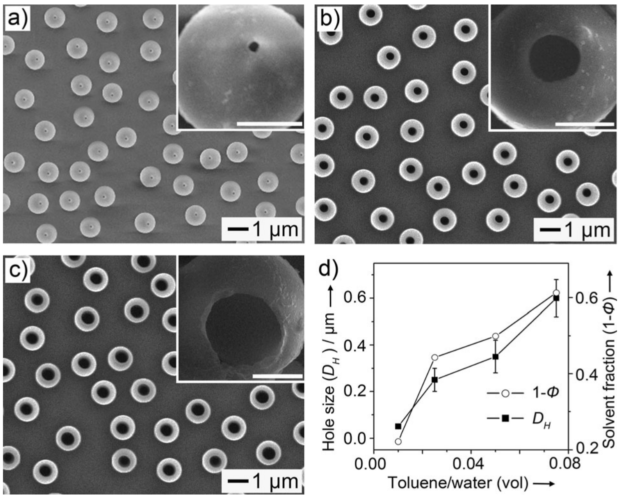

Figure 2. Control of the hole size by varying the volume ratio of toluene-to-water in the mixture used to swell the PS beads: a) 0.01, b) 0.05, and c) 0.075. The scale bars in the insets are 400 nm. d) Plots showing the changes to hole size (D_H) (■) and solvent volume fraction $(1-\phi)$ (○) as a function of toluene to water ratio. The solid lines are guides for the eyes. The amount of water was fixed at 2 mL.

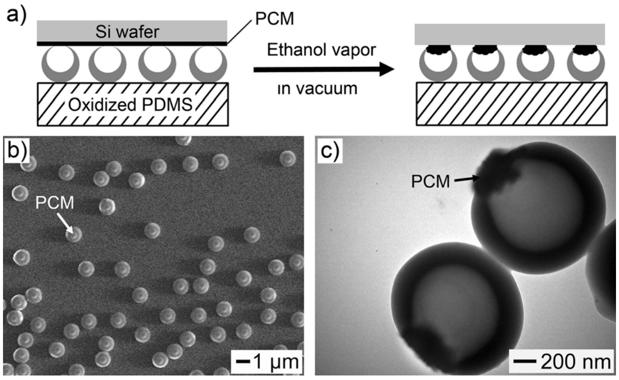

Figure 3. a) Schematic illustration of the procedure used to seal the holes on the surfaces of hollow particles with corks made of a PCM. See text for details. b) SEM and c) TEM images showing the particles corked with 1-tetradecanol.

To equip the particle with a thermosensitive response, we capped the hole with a cork made of a PCM. Figure 3 a shows an illustration of the corking procedure. A PCM/ethanol solution was spin-coated on a Si wafer. The resultant PCM film was then brought into contact with the hollow particles supported on a highly flexible PDMS substrate (40:1, w/w). The good flexibility led to a conformal contact between the particles and the PCM film, achieving essentially 100 % capping. Exposure of the sample to ethanol vapor allowed a viscous flow for the PCM, which could seal the holes under a vacuum state. Figure 3 b shows SEM image of PS hollow particles capped with 1-tetradecanol, which has a melting point (T_m) of 38–39 °C. The image clearly demonstrates that the holes on the particles were all capped by the PCM. The particles could even be released from the PDMS substrate by brief ultrasonication for TEM characterization. The ultrasonication was conducted in an ice water bath to prevent undesired melting of the PCM corks. As shown in Figure 3 c, the holes were still capped by the PCM corks, indicating that the seal was strong enough to tolerate the physical force of ultrasonication.

To demonstrate temperature-sensitive release with the particles, we used a fluorescent dye as the probe. The hollow particles (still on the PDMS substrate after the removal of P4VP matrix) were immersed in an aqueous solution of Rhodamine B under mechanical shaking. The sample was then taken out and dried in air. The hole on the surface of each particle allowed for easy, quick loading of the dye molecules into the void before it was sealed with a PCM-based cork. Figure 4 a and b, shows optical micrographs of the resultant particles after loading of the dye, drying, sealing of the holes with PCM, and washing of the sample to remove dye molecules adsorbed on the outer surface. The florescence micrograph in Figure 4 b verifies successful loading of Rhodamine B in the voids of all particles, indicating that the perfect capping prevented the removal of the loaded dye during washing of the sample. The loading content defined as a weight percentage of the dye, relative to the particles, was 0.72 %. The loading content can be easily increased by using Rhodamine B solution with a higher concentration for the loading process.[28]

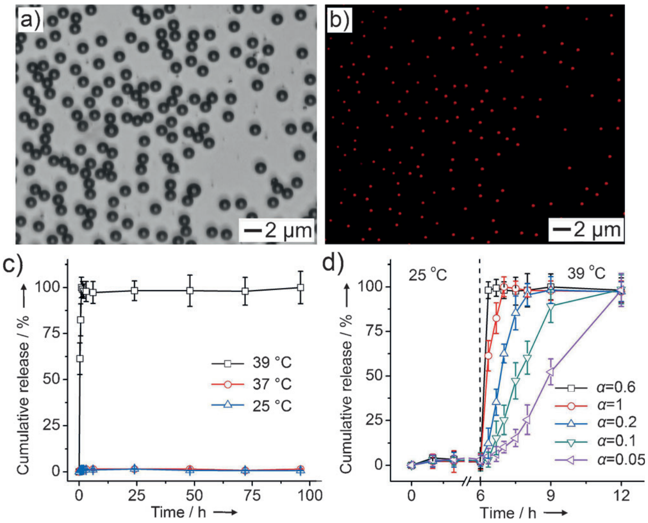

Figure 4. a) Optical and b) fluorescence micrographs showing fluorescence from Rhodamine B encapsulated in the hollow particles capped by a PCM. c) Release profiles at 25, 37, and 39 °C for Rhodamine B from the PS hollow particles capped by 1-tetradecanol in a buffer solution at pH 7.4. d) Release profiles of Rhodamine B from the particles capped by a binary mixture of PCMs consisting of 1-tetradecanol and lauric acid in a buffer solution at pH 7.4. The volumetric ratio (α) of 1-tetradecanol to lauric acid was varied from 0.05 to 1. The solid lines are guides for the eyes. Cumulative release (%) is defined as the amount of released dye at a given time divided by the maximum amount of released dye.

The Figure 4 c shows release profiles of Rhodamine B from the PS particles capped with 1-tetradecanol in a buffer solution at pH 7.4. Rhodamine B could not be released at 25 and 37 °C because the holes were perfectly sealed by solid 1-tetradecanol. The amount of Rhodamine B released over a period of 4 days was essentially negligible, which is different from other conventional systems that typically show a noticeable release at the initial stage due to free diffusion of the drug. At 39 °C, which is close to or slightly above the melting point (38–39 °C) of 1-tetradecanol, the PCM began to melt and then float on the surface of the buffer solution because of its low density and hydrophobicity.[19] As a result, the dye was instantly released through the re-opened holes on the particles. These results demonstrate that the release behavior could be regulated by taking advantage of the thermoresponsive property of a PCM. The temperature-regulated release was also kept in a buffer solution at pH 4.0 (see Figure S6). The result suggests that the PCM-corked particles had a good stability at low pH values.

Hydrophobic materials such as the majority of anticancer drugs can also be easily loaded in the voids inside the hollow particles.[28] The release will be (at least partially) governed by desorption of the drugs absorbed on the surface of the particles, leading to a different release profile. A systematic study is underway to investigate the release of hydrophobic drugs as a function of surface area, surface modification, and loading amount of the drugs.

We also used a binary PCM system with controllable melting points depending on the composition. In this case, lauric acid (T_m: 43.2 °C) was homogeneously mixed with 1-

tetradecanol at different ratios in weight and the mixtures were then employed as the corking materials. Both the 1-tetradecanol and lauric acid have very low toxicity in small doses because they are originally derived from natural fats and oils and thus are often used as ingredients for food and pharmaceuticals.[29] Administration of doses up to 10.0 $\mathrm{g\,kg^{-1}}$ of lauric acid by gavage to rats resulted in no deaths and no significant gross lesions at necropsy.[30] Although the minimal lethal or toxic dose of 1-tertadecanol has not been well established, the estimated acute fatal dose based on rat data is 80-200 g in an adult human case.[30]

Figure 4d shows the release profiles of Rhodamine B from the particles capped with binary PCMs with different weight ratios (α) of 1-tetradecanol to lauric acid in a buffer solution at pH 7.4. In all cases, the release of dye did not take place at 25 °C, indicating a successful sealing by the PCM mixtures. At 39 °C, Rhodamine B was released and the exact release profile depended on the ratio α. It took approximately 12 h for the sample with $\alpha = 0.05$ to complete the release. On the other hand, the fastest release was obtained at $\alpha = 0.6$, rather than for the sample with $\alpha = 1$, which consisted of only 1-tetradecanol. This result indicates that the melting behavior of the binary system did not monotonically change with the ratio of two PCMs. The phase diagram of 1-tetradecanol and lauric acid indicates that $\alpha = 0.6$ corresponds to an eutectic composition, at which the melting point is at a minimum value of 28.4 °C and both the components melted simultaneously.[31] It means that the mixture at $\alpha = 0.6$ would melt more rapidly, thereby yielding the fastest release. The phase diagram also gives a mass ratio (β) of liquid-to-solid phases for a given binary composition and temperature. For $\alpha = 0.2$, 0.1, and 0.05, the β values at 39 °C were 5.2, 0.3, and 0.14, respectively. Higher β values would provide more release paths, leading to faster release as shown in Figure 4d.

In summary, we have fabricated a thermosensitive system consisting of a hollow polymer particle with a hole on its surface, which could be sealed with a PCM cork after loading of molecules, macromolecules, or nanoparticles. We further demonstrated its use in temperature-regulated release of a dye. The temperature-sensitivity of the system arises from the PCM, which is capable of solid–liquid transition in response to temperature variation. The pre-loaded dye molecules could be encapsulated in the particles when the system was kept at a temperature below the melting point of the PCM whereas they could be released instantly at a temperature slightly higher than the melting point. The release profiles of the dye molecules could be further manipulated by using binary PCM systems.

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