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Assembly of MOF Microcapsules with Size-Selective Permeability on Cell Walls

*Wanbin Li, Yufan Zhang, Zehai Xu, Qin Meng, Zheng Fan, Shuaiju Ye, and Guoliang Zhang**

Abstract: *The assembly of metal–organic frameworks (MOFs) into microcapsules has attracted great interest because of their unique properties. However, it remains a challenge to obtain MOF microcapsules with size selectivity at the molecular scale. In this report, we used cell walls from natural biomaterials as non-toxic, stable, and inexpensive support materials to assemble MOF/cell wall (CW) microcapsules with size-selective permeability. By making use of the hollow structure, small pores, and high density of heterogeneous nucleation sites of the cell walls, uniform and continuous MOF layers could be easily obtained by inside/outside interfacial crystallization. The prepared MOF/CW microcapsules have excellent stability and enable the steady, slow, and size-selective release of small molecules. Moreover, the size selectivity of the microcapsules can be adjusted by changing the type of deposited MOF.*

Microcapsules have received much attention because of their potential applications in many fields, for example, for encapsulation[1] and catalysis,[2] as microreactors[3] and sensors,[4] and in drug delivery.[5] Polymers,[6] organometallic compounds,[7] coordination complexes,[8] and many other materials have been exploited to fabricate microcapsules. However, it is difficult to obtain microcapsules with size selectivity at the molecular scale.

Metal–organic frameworks (MOFs) are composed of small inorganic clusters connected by organic linkers.[9] They have uniform pores of molecular dimension, and have shown potential in the size-selective fabrication of microcapsules. Many studies have described the fabrication of hollow structured MOF materials with activity in catalysis and for encapsulation, for example,[10] but thus far, few have focused on MOF microcapsules with size-selective permeability.[11] Although free-standing MOF microcapsules that selectively release small molecules can be synthesized at the interface between immiscible metal salt and linker solutions, the assembly of defect-free MOF microcapsules with size-selective permeability in a facile, controllable, and scalable fashion still remains a challenge and is quite limited at present. Moreover, the weak mechanical stability of MOF materials will prevent the sustained application of free-standing microcapsules.[12]

As biomaterials usually have highly ordered architectures and diverse morphologies, in particular those with hollow structures,[13] we envisaged that by making use of a stable biomaterial with a hollow structure and a porous wall, the development of MOF microcapsules with size-selective permeability could be achieved. Cell walls of different microorganisms possess commendable hollow structures and small pores,[14] and exhibit excellent rigidity and strength.[15] They can be harvested easily, and the related materials are relatively inexpensive.[16] Moreover, as polar groups are abundant in biological macromolecules,[17] the compatibility of cell walls and MOFs can be easily improved.[18] Therefore, cell walls can be employed as a good support material for the fabrication of MOF microcapsules with size-selective permeability.

We herein report a strategy based on the use of cell walls to assemble MOF microcapsules with size-selective permeability by inside/outside interfacial crystallization (IOIC). Our method combines three key concepts: 1) the direct assembly of MOF layers on hollow structured cell walls to form microcapsules with size selectivity (Figure 1 a); 2) MOF

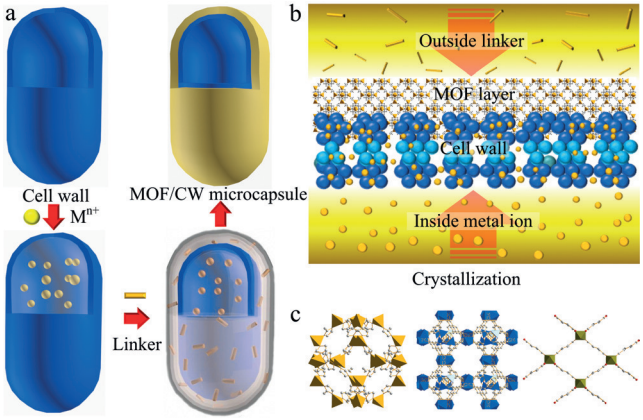

Figure 1. Assembly of MOF/CW microcapsules. a) Synthetic method for the deposition of a MOF layer on a cell wall. b) Crystallization of a MOF layer; while the metal ions are on the inside of the hollow cell wall, the linkers are on the outside. c) Crystal structures of ZIF-8, CuBTC, and MIL-53.

[*] Dr. W. Li, Z.H. Xu, Prof. Dr. Z. Fan, S. J. Ye, Prof. Dr. G. Zhang
Institute of Oceanic and Environmental Chemical Engineering
State Key Lab Base of Green Chemical Synthesis Technology
Zhejiang University of Technology
Hangzhou 310014 (P. R. China)
E-mail: guoliangz@zjut.edu.cn
Y. F. Zhang
College of Engineering, University of California
Berkeley, CA 94720 (USA)
Prof. Dr. Q. Meng
Department of Chemical and Biochemical Engineering
State Key Laboratory of Chemical Engineering
Zhejiang University
Hangzhou 310027 (P. R. China)

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crystallization between the separated metal salt (inside the cell) and linker (outside the cell) with no requirement for two immiscible solvents (Figure 1 b); and 3) preferential growth of MOF crystals on cell walls arising from the good affinity between the biological macromolecules and ions. This strategy is applicable to a broad range of MOFs and cell walls from various biomaterials. The assembled MOF microcapsules display good stability and enable the steady size-selective release of small molecules. Furthermore, the size-selective permeability of the microcapsules can be adjusted by changing the type of coated MOF.

We first employed the representative MOFs ZIF-8[19] and CuBTC[20] to demonstrate the feasibility of exploiting cell walls to assemble MOF microcapsules. Yeast,[21] which is the most widely used fungus in the world, was selected as the main probe in this study for safety reasons. Before synthesis, the yeast was washed with hot water and methanol several times to remove the cytoplasm and to obtain the pure cell wall. A transmission electron microscopy (TEM) image confirms that a hollow structure was thus obtained (Supporting Information, Figure S1). The assembly method by IOIC is illustrated in Figure 1. The hollow cell-wall structure was impregnated with metal ions by immersion into a metal salt solution. Then, the cell wall containing metal ions was isolated and added to a linker solution for crystallization at 323 K under gentle stirring. For the synthesis of CuBTC/CW microcapsules, the color change of the reaction mixture was notable (Figure S2). The cell-wall suspension was creamy white. When the copper salt was added, the color of the suspension changed to light blue. Once the cell wall had been isolated and added to another solution, the suspension remained light blue at the beginning and then became dark blue after stirring for twelve hours. After a second round of centrifugation, a blue precipitate and the transparent supernatant were obtained. This finding indicates that the copper ions had been absorbed by the cell wall and used for CuBTC synthesis. ZIF-8/CW microcapsules were also fabricated according to the same method.

Scanning electron microscopy (SEM) images of the two kinds of microcapsules are shown in Figure 2 a, c. Compared with the smooth surface of the pure cell wall (Figure S1), we now observed continuous and intergrown MOF layers tightly covering the surface of the cell wall. The MOF crystals were very small, for example, the ZIF-8 crystals were 20–80 nm large, with an average diameter of 47 nm (Figure S3), which is much smaller than that of other MOF microcapsules reported elsewhere.[11] The SEM images also indicate that the MOF/CW microcapsules are well dispersed and uniform, with diameters of approximately 3–7 μm (Figure S4). We further characterized the MOF/CW microcapsules by TEM. The bright parts in the center of the TEM images confirm the hollow structures of the microcapsules (Figure 2 b, d). Moreover, the microcapsules were dispersed in methanol and characterized by optical microscopy. The images also reveal hollow structures. To visually characterize the inner structures, the MOF/CW microcapsules were grinded, and hollow spherical fragments could be clearly observed. X-ray diffraction (XRD) was employed to investigate the crystalline structure of the MOFs on the cell walls. The cell wall gives rise

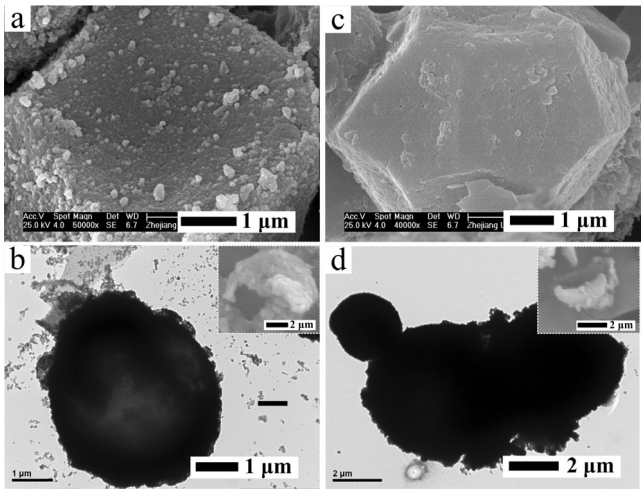

Figure 2. SEM (a, c) and TEM (b, d) images of ZIF-8/CW microcapsules (a, b) and CuBTC/CW microcapsules (c, d).

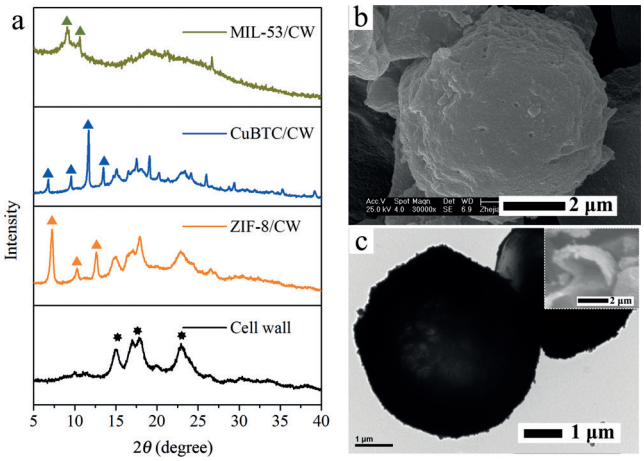

Figure 3. a) XRD patterns of the MOF/CW microcapsules. b) SEM and c) TEM images of the MIL-53/CW microcapsule.

to several peaks with 2θ values of 15–25° (Figure 3 a), which demonstrates that the structure of the cell wall is not completely amorphous. After MOF growth, characteristic MOF peaks were detected, which closely correspond to those of previous reports,[19] demonstrating the high phase purity and homogeneity of the MOF/CW microcapsules. As the concentration of the precursor solution is usually very important for the synthesis of a MOF film,[22] we increased the concentrations of the metal ion and linker solutions. As expected, with an increase in concentration, the ZIF-8 crystals became larger (Figure S5). At all concentrations tested, the obtained MOF layers were always continuous and intergrown.

During conventional interfacial synthesis from two immiscible solutions, high precursor concentrations are usually required to increase the reaction rate to prevent one precursor from entering the other solution, which would cause the production of bulk nuclei and lead to the formation of discontinuous frameworks or even prevent MOF micro-

capsule formation. However, in our strategy, because of the abundance of polar groups in the cell walls, the crystals will preferentially grow on the porous walls. Moreover, the pore sizes of cell walls are small,[14,21] which will reduce the diffusion rates of the precursors. Therefore, even at low precursor concentrations, microcapsules with continuous MOF layers can be obtained.

To illustrate the chemical stability of the cell wall, which is very important for the application of the synthesized MOF/CW microcapsules, we employed the MOF MIL-53 to fabricate MOF/CW microcapsules. MIL-53, which consists of Fe^{III} ions and terephthalic acid, is another commonly studied MOF.[23] Compared with ZIF-8 and CuBTC, the synthesis of MIL-53 generally requires much more rigorous conditions, namely a reaction temperature of 423 K and *N*,*N*-dimethylformamide (DMF) as the solvent. After synthesis, a SEM image revealed that the cell wall had maintained its hollow microcapsule structure (Figure 3b and Figure S4). Compared with the pure cell wall, we also observed that a continuous MIL-53 layer covered the surface of the cell wall. The XRD pattern of the microcapsule demonstrates that the crystal is MIL-53. However, because of the synthesis conditions, the crystalline phase is not as pure as that of ZIF-8 or CuBTC. For comparison, we tried to synthesize pure ZIF-8, CuBTC, and MIL-53 under the same conditions as for the MOF/CW microcapsules. It was found that ZIF-8 and CuBTC, but not MIL-53, could be prepared successfully, (Figure S6). This finding illustrates that the synthesis of MOFs by IOIC on cell walls can greatly improve the crystallinity of the MOFs. These results also reveal that cell walls can be exploited to improve the synthesis of MOF microcapsules, which usually requires harsh reaction conditions, and that the assembled MOF/CW microcapsules can be used in aggressive solvents.

To confirm that our method is not limited to the cell walls of fungi, *Escherichia coli*, harmless bacteria, were also employed to prepare MOF microcapsules. As shown in Figure S7, we achieved the synthesis of a continuous, uniform MOF layer on the cell wall of *Escherichia coli*. Moreover, the microcapsules were much smaller than those obtained when yeast cell walls were employed. Because of the amorphous structure of the cell wall, the hollow structure of the microcapsule could not be confirmed by TEM. These results, combined with the deposition of different MOFs on the cell wall of yeast, demonstrate that our method has general applicability.

To validate the continuity and selectivity of the MOF/CW microcapsules, several small organic reagents with different sizes were loaded onto the MOF/CW microcapsules for controllable release. Theoretically, if the MOF layers are continuous and completely defect-free, molecules that are larger than the aperture of the framework cannot leave the microcapsules. Otherwise, these molecules could diffuse through the walls of the microcapsules. In our experiment, three molecules (rhodamine B (RB), methyl red (MR), and salicylic acid (SA)) were used as probe molecules (Figure S8). First, RB was encapsulated in MOF/CW microcapsules. The RB content was obtained by removing the MOF layers through dissolution in acid. The microcapsules were

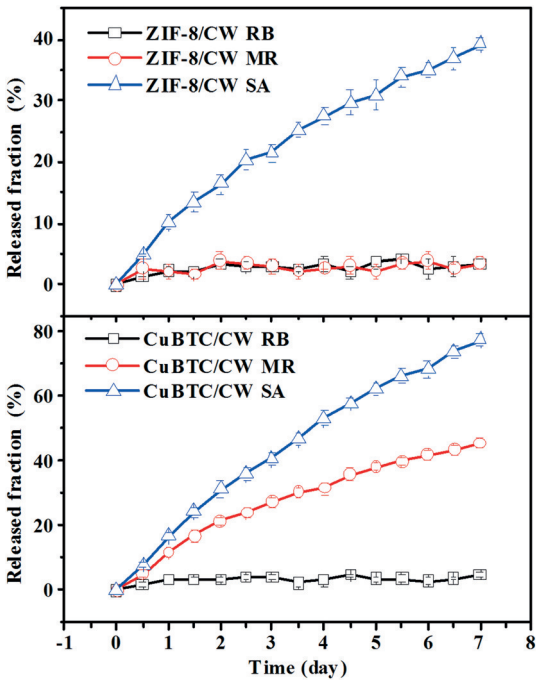

Figure 4. Size-selective permeability of a) ZIF-8/CW and b) CuBTC/CW microcapsules.

immersed in methanol under stirring.[1b] The release of RB from the microcapsules into solvent was monitored over time (Figure 4 and Figure S9). For all the ZIF-8/CW, CuBTC/CW, and MIL-53/CW microcapsules, hardly any RB was released. This result demonstrates there were no defects in the MOF layers that were large enough to allow RB to escape from the microcapsules. To investigate the long-time stability of the MOF/CW microcapsules, the release time was extended to 20 days, and again, hardly any RB could be detected in the surrounding solvent (Figure S9). This result confirms that the ZIF-8/CW, CuBTC/CW, and MIL-53/CW microcapsules had excellent long-time stability. As expected, when we removed the MOF layers, extremely rapid release was observed, and nearly all RB was released within several hours, which showed that the mass transfer resistance can be attributed mainly to the continuous MOF layers. To determine whether RB was located in the microcapsule interiors or in the pores of the MOFs, we synthesized RB-loaded MOF particles and characterized their RB content. The UV/Vis absorbance of RB-loaded MOF particles was much smaller than that of the MOF/CW microcapsules (Figure S10), demonstrating that RB was mainly incorporated into the interior of the microcapsules, rather than immobilized in the pores of the MOFs.

MR was also encapsulated in the MOF/CW microcapsules for controlled release. The release profile of the ZIF-8/CW microcapsules was similar to that of the MOF/CW microcapsules for RB, and almost no MR was found in the surrounding solvent after stirring for seven days. It seemed that MR was also not able to pass through the wall of ZIF-8/CW microcapsules. However, about 46% of MR had been released from CuBTC/CW microcapsules after seven days. The reason for this phenomenon is that CuBTC has a larger aperture (0.9 nm) than ZIF-8 (0.34 nm), which is bigger than

the size of MR. Independent of the MOF microcapsule used, SA was always released from the microcapsules. After seven days, 78% and 39% of the SA had been released into the surrounding solvent from CuBTC/CW and ZIF-8/CW microcapsules, respectively. Consistent with common theory, CuBTC/CW microcapsules, which have larger apertures, have a faster release rate than ZIF-8/CW microcapsules, which feature smaller apertures. It should be noted that the kinetic diameter of SA is larger than the aperture of ZIF-8, but the molecule can nevertheless pass through the wall of ZIF-8/CW microcapsules. This may be the result of the well-known lattice flexibility of ZIF-8. Compared with other studies,[11,24] our MOF/CW microcapsules go through a more stable and slower release process, which indicates that MOF/CW microcapsules have good potential for drug delivery. The release behavior of these microcapsules demonstrates that the MOF layers of the MOF/CW microcapsules are continuous, and that the MOF microcapsules prepared herein can be applied for controlled release with molecular selectivity. Moreover, the molecular weights of the reagents that can pass through the microcapsule walls are different for various MOFs.

In conclusion, by making use of the hollow structure and the high density of heterogeneous nucleation sites of cell walls, we have achieved the synthesis of MOF microcapsules with size-selective permeability on cell walls by inside/outside interfacial crystallization in a simple, versatile, and scalable process. Our strategy is applicable to a broad range of MOFs and microorganisms. The assembled microcapsules have a uniform and defect-free MOF layer and display excellent solvent resistance and long-time stability. The microcapsules can reject large molecules, and release small molecules steadily and slowly. Moreover, the size selectivity of the microcapsules can be adjusted by changing the type of deposited MOF. The features presented herein suggest that microcapsules made from natural biomaterials with highly ordered architectures will be promising materials for various applications.

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Keywords: cell walls · metal–organic frameworks · microcapsules · permeability

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