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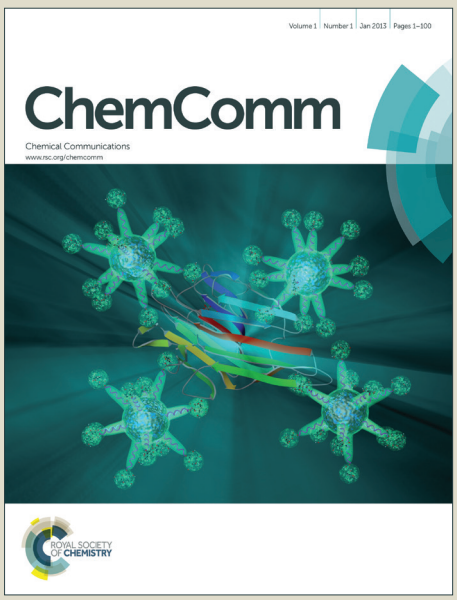

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ARTICLE TYPE

Janus molecularly imprinted polymer particles

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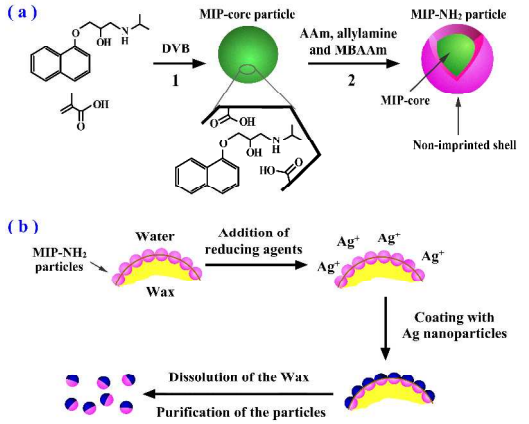
By combining the specific molecular recognition capability of MIPs and the asymmetric structure of Janus particles, the Janus MIP particles which were synthesized *via* a wax/water Pickering emulsion showed attractive capabilities as Self-propelled Transporters for controlled drug delivery.

Because of the asymmetric dual functions, Janus particles have been widely used as solid stabilizers, imaging probes, targeting sensors, interfacial catalysts, and photonic materials in various fields.[1] Generally, Janus particles could be prepared using a variety of techniques. In the beginning, the most traditional strategy to synthesize Janus particles was a two-dimensional approach: particles were deposited onto a substrate and then their above surface was coated with metals.[2] As an extension of this concept, Pickering emulsion has recently been reported to obtain larger quantities of Janus beads. In this concept, a wax in water emulsion was often chosen as the Pickering emulsion system.[3] Recently, block copolymer self-assembly method, phase separation method, competitive adsorption method, and the integration of microfluidic devices and photolithographic polymerization or photopolymerization have been widely used to control the structural variety of Janus particles.[4]

Using the above strategies, the anisotropic functions of Janus particles can be successfully controlled. However, it is still difficult to selectively load chemical or biological components such as drugs, dyes, probes, and image contrasting agents onto the Janus particles.[5] This disadvantage limits the practical application of the Janus particles. Therefore, it is a significant challenge to selectively load/unload a target agent onto the Janus particles.

The best way to achieve specific molecular loading/unloading is molecular imprinting.[6] It is known that molecular imprinting is a synthetic technology, which allows the preparation of homogeneous polymeric matrices with specific binding cavities.[7] The main advantages of molecularly imprinted polymers (MIPs) are their high selectivity and affinity to the template molecules used in the imprinting procedure. Therefore, MIPs have found many practical applications, including separation and purification, chemical sensors, catalysis, drug delivery, plastic antibodies and biological receptors system.[8]

In this work, a new method was developed to construct Janus particles with specific molecular recognition ability. It has been reported that, the presence of amine groups on the MIP particles is in favour of coating Ag nanoparticles (NPs) onto MIP particles.[9] Here, monodisperse MIP particles containing amino groups (MIP-NH_2 particles) were synthesized *via* a two-step precipitation polymerization (Scheme 1a) following a similar procedure described by Hajizadeh et al.[10]



Scheme S1. (a) Schematic representation of the synthesis of monodisperse MIP-NH_2 microspheres. Step 1: generation of propranolol-imprinted sites by cross-linking polymerization. Step 2: grafting amine groups by copolymerization. (b) Step-by-step fabrication of Janus colloidal particles.

Pickering emulsion is an emulsion stabilized by solid particles instead of surfactants.[11] Recently, complex colloid-based materials prepared by Pickering emulsion have attracted more and more interests.[12] For example, we have previously prepared several types of MIP beads and MIP colloidosomes using different Pickering emulsion systems.[13] In the present work, we also used Pickering emulsion to synthesize Janus MIP particles. The schematic representation of the step-by-step synthesis of Janus MIP particles was shown in Scheme 1b. First, monodisperse MIP-NH_2 particles were used as fine solid particles to stabilize the molten wax in water emulsion at a high temperature. When the emulsion system was cooled down, the MIP-NH_2 particles were immobilized at the solidified interface. In water phase, the exposed surface of the MIP-NH_2 particle was coated with silver NPs by adding reducing agents. After dissolving the wax, the Janus MIP particles were obtained by centrifugation. There are two main reasons for synthesis of Janus MIP particles *via* Pickering emulsion. The first one is that this method offers controllable morphology in a wide range of size and surface functionality of the particles.[14] The second one is that the molecular recognition cavities could be always generated under the optimal imprinting conditions in this method.

To confirm the synthesis of Janus MIP particles, the surface

groups of the particles were studied by FT-IR analysis. In comparison with MIP-core particles, the MIP-NH_2 particles containing a NIPA-allylamine-MBAAm copolymer shell showed several obvious changes, indicating that the Ag NPs were tightly coated onto MIP-NH_2 particles through hydrogen bond (see ESI). In the UV-vis spectra, the Janus MIP particles displayed an obvious surface plasmon resonance absorption band (at 409 nm), further indicating that the MIP-NH_2 particles were perfect carriers for the formation of Ag NPs (see ESI).[15] The TGA measurements indicate that the weight proportion of Ag NPs on the Janus particles was 8.6% (see ESI). The surface morphology of the MIP-NH_2 particles and the Janus MIP particles was observed by SEM. Fig. 1a and Fig. S3a are the SEM images of the MIP-NH_2 particles. From these figures, it is seen that the MIP-NH_2 particles were monodisperse with a size of 2.0 μm. Fig. 1b and Fig. S3b are the SEM images of the Janus MIP particles. It is seen that the formation of Ag nanostructures onto one side of the MIP-NH_2 particles could be controlled during the synthesis. The scale up of the particle shown in Fig. 1b looks like metal cap-wearing particles, which would have great potential in sensors, anisotropic building blocks, and osmotic motors.

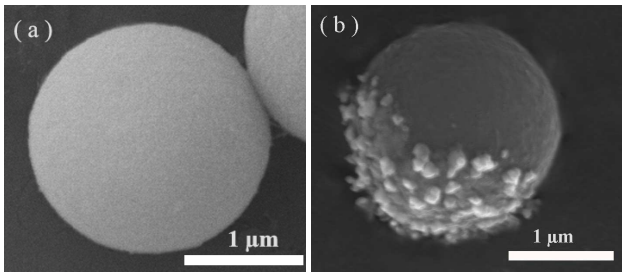


Fig. 1 SEM images of the MIP-NH_2 (a) and the Janus MIP (b) particles.

The binding profile of the Janus MIP particles was evaluated by using tritium-labeled propranolol as a probe through radioligand binding analysis. Simultaneously, the binding profiles of the Janus NIP particles, the MIP-NH_2 particles and the NIP-NH_2 particles were also investigated as controls. Fig. 2a displays the uptake of [^{3}H]-(*S*)-propranolol by the different particles. It is seen that the propranolol uptake by the Janus MIP particles was much higher than that by the Janus NIP particles, suggesting that the Janus MIP particles possessed available molecular binding cavities. Moreover, the binding profile of the Janus MIP particles was very similar to that of the MIP-NH_2 particles, indicating the asymmetric coating of Ag NPs onto the MIP particles did not decrease the specific binding capacity.

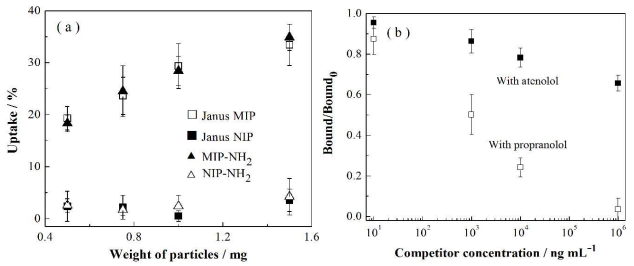


Fig. 2 (a) Equilibrium radioligand binding analysis. (b) Displacement of radioligand binding to 0.5 mg of Janus MIP particles with increasing amount of atenolol and propranolol. $Bound_0$ and Bound are the amount of [^{3}H]-(*S*)-propranolol bound by Janus MIP in the absence and presence of the competing compounds, respectively.

Molecular selectivity of the Janus MIP particles was also investigated using a competitive radioligand binding. The competitive binding curve by the Janus MIP particles was shown in Fig. 2b. It is seen that the increasing of the competitors decreased the uptake of the template binding on the Janus MIP particles. However, the potency of the structural analog (atenolol) to displace the radioligand from the Janus MIP particles was much lower than the potency of propranolol. This molecular selectivity study verifies that the Janus MIP particles remained the easily accessible binding sites.

In previous studies, sell-propelled Janus particle has been studied for different systems.[16] Accordingly, when the Janus MIP particles are exposed to the UV light in the presence of H_2O_2, an ion gradient will be formed due to the production of Ag^+ and HOO^- ions in the solution, and the Janus MIP particles will move in their self-generated ion gradient along their axis with the Ag particle leading.[16a] Therefore, by introducing Janus structures to molecular imprinting, MIPs represent an attractive route for creating specific molecular recognition cavities in synthetic self-propelled nano or micro engines. To the best of our knowledge, only a single research paper investigated the MIP microtransporter,[17] where the MIP-based catalytic microtubular engines were prepared by electropolymerization of the MIP layer onto Pt-Ni microengines. In this work, we provided another type of MIP microtransporter based on the Janus MIP particles. Because of the using of the modular MIP building blocks (monodisperse MIP microspheres synthesized by precipitation), the Janus MIP particles showed an important advantage: the molecular recognition cavities were generated always under optimal imprinting conditions.

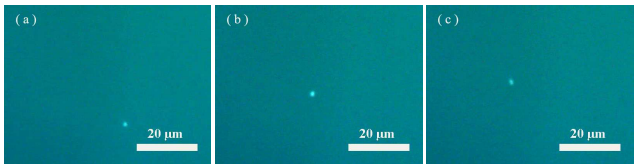


Fig. 3 Real-time optical microscopy images of a Janus MIP particle in 2.5% H_2O_2 with UV light (254 nm), showing the trajectory at: (a) t=0 s, (b) t=2 s and (c) t=4 s. Scale bar=10 μm.

Fig. 3 shows the movements and the phototactic response of the Janus MIP particle in H_2O_2. In this figure, the silver-leading autonomous motion was clearly observed on the Janus MIP particles. However, the diffusiophoretic movement was not found when the MIP-NH_2 particles were placed under the same condition (Fig. S4), which indicates that the motion of the MIPs significantly depended on the asymmetry coating of Ag NPs. The path of a single Janus MIP particle in the presence of H_2O_2 with or without UV light illumination is shown in Fig. 4a. It is seen that the diffusiophoretic movement of the Janus MIP particle could be controlled by turning on/off the UV light (Fig. S5 and Video S1). When UV light was switched on (from t=0 s to t=30 s), the Janus MIP particle moved fast with an observed speed of 3 μm/s approximately. After turning off the UV light (from t=31s to t=40 s), the movement of the Janus MIP particle was slow and irregular. This movement might be the thermal Brownian motion.[16c] When the UV light was re-switched on (from t=41 s to t=70 s), the Janus MIP particle moved again with a similar speed. These experimental data confirm the Janus MIP particles were

easy to handle in practical applications as microtransporters.

The microtransporters could be used as autonomous carriers for controlled drug delivery. Here, we investigated propranolol release from the polymer particles in H_2O_2 solution with or without UV illumination, as shown in Fig. 4b. It is seen that the Janus NIP particles were bad carriers for propranolol delivery because of their low loading capacity. It had been reported that Janus particles exhibited a variety of complex and partially unexpected aggregate,[18] therefore the Janus MIP particles showed a low drug release process in the presence of H_2O_2 without UV illumination. Likewise, the MIP-NH_2 particles showed a relatively slow release of propranolol. However, when the Janus MIP particles were used as autonomous carriers in the presence of H_2O_2 with UV illumination, the Janus MIP particles were moved continuously by the mechanism of diffusiophoresis. Both the surface charge and the autonomous movement could be seen as possible factors to enhance the dispersion of the particles, which hence accelerated the drug diffusion in the release medium.[16a] Therefore, MIP cavities provides the Janus MIP particles with high loading capacity, while the asymmetry structure of the Janus MIP particles played an important role during the controlled-release process. Interestingly, the drug delivery from the Janus MIP particles can be controlled by the switch on/off the UV illumination.

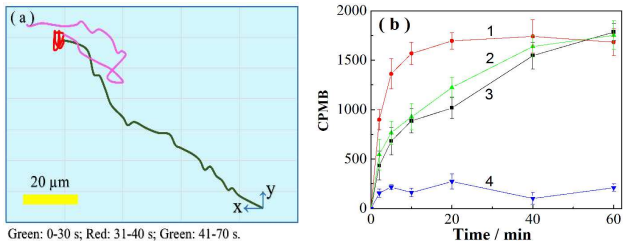


Fig. 4 (a) Recorded path of Janus MIP particles according to the configurations shown in Fig. 3. Fuel: 2.5% v/v H_2O_2. (b) Propranolol release curve from the Janus MIP particles in the presence of H_2O_2 and with UV illumination (1), from the Janus MIP particles in the presence of H_2O_2 and without UV illumination (2), from the MIP-NH_2 particles in the presence of H_2O_2 and with UV illumination (3), and from the Janus NIP particles in the presence of H_2O_2 and with UV illumination (4). Counts per minute B (CPMB) is a measurement of the detection rate of ionization events per minute in Region B.

In summary, a novel type of Janus MIP particles has been synthesized using a wax/water Pickering emulsion based on the modular MIP building blocks. When tailor-made recognition cavities were introduced into catalytic microengine transporters, the Janus MIP particles could be readily extended to the selective separation of the target analytes as well as the construction of self-propelled objects. This molecularly imprinted micro-transporter concept provided the Janus MIP particles with attractive capabilities for autonomous binding, controlled transport, and separation of the target analytes. Due to the fact that Ag NPs have poor biocompatibility and UV illumination (or H_2O_2) damages cells, the Janus MIP particles prepared here showed some limitations in the practical application. However, by coating other metal alloy NPs,[19] biocompatible Janus MIP particles (which can harvest energy without UV illumination or H_2O_2) can be generated to address this problem. The drug delivery system based on the biocompatible Janus MIP particles will be applied in the realistic examples in our future work.

Notes and references

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1 A. Walther and A. H. E. Müller, *Chem. Rev.*, 2013, **113**, 5194.
2 J. Du and R. K. O'Reilly, *Chem. Soc. Rev.*, 2011, **40**, 2402.
3 (a) S. Jiang and S. Granick, *Langmuir*, 2008, **24**, 2438; (b) J. Hu, S. Zhou, Y. Sun, X. Fang and L. Wu, *Chem. Soc. Rev.*, 2012, **41**, 4356; (c) S. Jiang, Q. Chen, M. Tripathy, E. Luijten, K. S. Schweizer and S. Granick, *Adv. Mater.*, 2010, **22**, 1060.
4 (a) M. Lattuada and T. A. Hatton, *Nano Today*, 2011, **6**, 286; (b) A. Perro, S. Reculusa, S. Ravaine, E. Bourgeat-Lami and E. Duguet, *J. Mater. Chem.*, 2005, **15**, 3745; (c) D. Dendukuri and P. S. Doyle, *Adv. Mater.*, 2009, **21**, 4071; (d) Z. Yu, C.-F. Wang, L. Ling, L. Chen and S. Chen, *Angew. Chem. Int. Ed.*, 2012, **51**, 2375.
5 C. Y. Jung, J. S. Kim, H. S. Kim, J. M. Ha, S. T. Kim, H. J. Lim and S. M. Koo, *J. Colloid Interface Sci.*, 2012, **367**, 257.
6 (a) G. Wulff, *Chem. Rev.*, 2002, **102**, 1; (b) L. Ye and K. Mosbach, *Chem. Mater.*, 2008, **20**, 859; (c) X. Shen, L. Zhu, J. Li and H. Tang, *Chem. Commun.*, 2007, 1163; (d) S. C. Zimmerman, M. S. Wendland, N. A. Rakow, I. Zharov and K. S. Suslick, *Nature*, 2002, **418**, 399.
7 (a) G. Pan, Y. Zhang, Y. Ma, C. Li and H. Zhang, *Angew. Chem. Int. Ed.*, 2011, **50**, 11731; (b) Y. Yu, L. Ye, K. Haupt and K. Mosbach, *Angew. Chem. Int. Ed.*, 2002, **41**, 4459; (c) Y. Hoshino, H. Koide, T. Urakami, H. Kanazawa, T. Kodama, N. Oku and K. J. Shea, *J. Am. Chem. Soc.*, 2010, **132**, 6644; (d) X. Shen, L. Zhu, G. Liu, H. Yu and H. Tang, *Environ. Sci. Technol.*, 2008, **42**, 1687; (e) J. L. Urraca, C. S. A. Aureliano, E. Schillinger, H. Esselmann, J. Wiltfang and B. Sellergren, *J. Am. Chem. Soc.*, 2011, **133**, 9220.
8 (a) L. Li, Y. Lu, Z. Bie, H.-Y. Chen, Z. Liu, *Angew. Chem. Int. Ed.*, 2013, **52**, 7451; (b) K. Golker, B. C. G. Karlsson, G. D. Olsson, A. M. Rosengren and I. A. Nicholls, *Macromolecules*, 2013, **46**, 1408; (c) I. S. Chronakis, A. Jakob, B. Hagström and L. Ye, *Langmuir*, 2006, **22**, 8960.
9 L. Ramajo, R. Parra, M. Reboredo and M. Castro, *J. Chem. Sci.*, 2009, **121**, 83.
10 S. Hajizadeh, C. Xu, H. Kirsebom, L. Ye and B. Mattiasson, *J. Chromatogr. A*, 2013, **1274**, 6.
11 (a) Pickering, S. U. *J. Chem. Soc., Trans.*, 1907, **91**, 2001; (b) S.-H. Kim, S. Y. Lee and S.-M. Yang, *Angew. Chem., Int. Ed.*, 2010, **49**, 2535; (c) A. D. Dinsmore, M. F. Hsu, M. G. Nikolaides, M. Marquez, A. R. Bausch and D. A. Weitz, *Science*, 2002, **298**, 1006.
12 A. Schrade, K. Landfester and U. Ziener, *Chem. Soc. Rev.*, 2013, **42**, 6823.
13 (a) X. Shen and L. Ye, *Macromolecules*, 2011, **44**, 5631; (b) X. Shen and L. Ye, *Chem. Commun.*, 2011, **47**, 10359; (c) X. Shen, C. Xu and L. Ye, Soft Matter, 2012, **8**, 7169. (d) X. Shen, T. Zhou and L. Ye, *Chem. Commun.*, 2012, **48**, 8198. (e) X. Shen, C. Xu, K. M. A. Uddin, P.-O. Larsson and L. Ye , *J. Mater. Chem. B*, 2013, **1**, 4612.
14 (a) B. Liu, W. Wei, X. Qu and Z. Yang, *Angew. Chem. Int. Ed.*, 2008, **47**, 3973; (b) A. Walther and A. H. E. Müller, *Soft Matter*, 2008, **4**, 663.
15 L. Xie, M. Chen and L. Wu, *J. Polym. Sci. Part B: Polym. Chem.*, 2009, **47**, 4919.
16 (a) A. Sen, M. Ibele, Y. Hong and D. Velegol, *Faraday Discuss.*, 2009, **143**, 15; (b) S. Gangwal, O. J. Cayre, M. Z. Bazant, O. D. Velev, *Phys. Rev. Lett.*, 2008, **100**, 058302. (c) N. Chaturvedi, Y. Hong, A. Sen and D. Velegol, *Langmuir*, 2010, **26**, 6308.
17 J. Orozco, A. Cortés, G. Cheng, S. Sattayasamitsathit, W. Gao, X. Feng, Y. Shen and J. Wang, *J. Am. Chem. Soc.*, 2013, **135**, 5336.
18 (a) Y. Hong, M. Diaz, U. M. Córdova-Figueroa and A. Sen, *Adv. Funct. Mater.*, 2010, **20**, 1568. (b) Z.-W. Li, Z.-Y. Lu, Y.-L. Zhu, Z.-Y. Sun and L.-J. An, *RSC Adv.*, 2013, **3**, 813.
19 (a) W. Gao, A. Pei and J. Wang, *ACS Nano*, 2012, **6**, 8432. (b) W. Gao, X. Feng, A. Pei, Y. Gu, J. Li and J. Wang, *Nanoscale*, 2013, **5**, 4696.