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Microfluidic synthesis and on-chip enrichment application of two-dimensional hollow sandwich-like mesoporous silica nanosheet with water ripple-like surface

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Abstract

The merits of microfluidics bring new opportunities for engineering of nanomaterials with well controlled chemical, physical and biological properties for a variety of applications. Herein, using a two-run spiral-shaped microfluidic device, we first develop a facile and straightforward flow synthesis strategy to create two-dimensional mesoporous silica nanosheet (MSN). Such MSN exhibits typical hollow sandwich-like bilayer and unique water ripple-like wrinkle surface, which greatly increase the particulate accessibility for mass transfer. The enhanced on-chip enrichment performance of MSN is further confirmed toward different substrates (dye, protein, drug). These findings not only shed new light on microfluidics-enabled chemicals engineering, but also open up numerous new possibilities by microfluidics in adsorption, separation, and biomedical fields.

Keywords

Microfluidics; Two-dimensional; Microreactor; Nanosheet; Surface pattern

1. Introduction

Mesoporous silica materials have emerged as an important class of nanoporous materials since their discovery in the early 1990s.^[1] In comparison with other types of porous materials, mesoporous silica exhibits many distinctive features such as robust thermal and mechanical stability, good biocompatibility, large specific surface area, high pore volume, and especially the unprecedented flexibility in rational control of particle size, shape, pore, and surface functionality, making them ideal candidates for mass transfer and molecular diffusion.^[2] However, most of mesoporous silica materials reported to date possess only single or simple architectures that generally do not allow rapid and efficient enrichment of molecules of interest, and thus their potential applications are limited.^[3] The introduction of

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ASSOCIATED CONTENT

Supporting Information Available: Materials characterization, standard curves, and additional data.

multilevel properties into mesoporous silica can markedly improve its accessibility and expand its use as host materials. Despite the great needs, it is noted that there are still very limited methods reporting on the synthesis of multilevel mesoporous silica materials, especially those having low-dimensional framework and rich porous texture,^[4–6] from conventional batch reactors. Therefore, facile and scalable synthesis of uniform mesoporous silica materials with two-dimensional anisotropic structure remains an outstanding challenge.

In recent years, the emergence of microfluidic techniques provides new opportunities for engineering of nanomaterials and their corresponding applications.^[7–11] From novel materials development point of view, microfluidics-based microreactors could exhibit many appealing features that conventional batch reactors can hardly achieve. These include, but are not limited to: 1) greatly reduced mixing time down to the order of microseconds or even less due to the chaotic advection effect; 2) extremely minimized local variations with automated operations and reduced reactor dimensions; 3) large surface-to-volume ratio of microchannels for enhancing mass and heat transfer; 4) sufficient mixing of chemical reactants for achieving high yield of product; 5) rapid reaction kinetics for fast screening of synthesis parameters; 6) confining potentially toxic, corrosive, flammable, or explosive starting materials into a small space for providing great chances to create new particulate structures.^[12,13] Meanwhile, the merits of high throughput, low cost, high flexibility, automation capability, and enhanced spatio-temporal control allow microfluidics to serve as a promising platform in diverse application fields, such as biosensing,^[10] pharmaceuticals,^[14] catalysis,^[15] tissue engineering,^[16] and liquid biopsy.^[8]

In this study, using a short-range spiral-shaped microfluidic device with two runs, we first created two-dimensional mesoporous silica nanosheet (MSN) and examined its on-chip enrichment performance toward different substrates (Figure 1). The formation of MSN was driven by two inlet reactant flows, one containing diluted Tetraethyl orthosilicate (TEOS) in ethanol and the other Cetyltrimethylammonium bromide (CTAB) and Tetrabutylammonium iodide (TBAI) in diluted ammonia. Such two-dimensional mesoporous nanosheet exhibits typical hollow sandwich-like bilayer structure and unique water ripple-like wrinkle surface. These inherent advanced properties of MSN together with the promising features of microfluidics permit greatly enhanced enrichment performance.

2. Experimental details

2.1 Materials and reagents

Tetraethyl orthosilicate (TEOS), Cetyltrimethylammonium bromide (CTAB), Tetrabutylammonium iodide (TBAI), ammonium hydroxide (25%), ethanol (200-proof), Rhodamine B (RB), bovine albumin-fluorescein isothiocyanate conjugate, bovine serum albumin, doxorubicin hydrochloride (Dox) were purchased from Sigma-Aldrich. Polydimethylsiloxane (PDMS Sylgard 184) was purchased from Dow Corning. Water used was from a Milli-Q water ultrapure water purification system. All chemicals were used as received without any further purification.

2.2 Fabrication of two-run spiral-shaped microfluidic reactor

The two-run microfluidic spiral channel with two inlets and one outlet was fabricated using soft lithography. Briefly, film mask was designed with AutoCAD software and ordered from Fine Line Imaging, Inc.. Then, the master mold was fabricated with standard photolithography. After that, the PDMS precursor was poured over it, left to solidify at 65 °C for 1 hour and peeled off to get the replica. Microchannels were formed by bonding the oxygen plasma treated PDMS replica to a standard glass slide. The spiral-shaped microchannel is made of three arcs with the diameters of 7.69 mm, 13.8 mm, and 22.2 mm, with the central angles of 180°, 180°, and 225°, respectively. The width and height of the microchannel are 500 µm and 50 µm, respectively.

2.3 Synthesis of two-dimensional mesoporous silica nanosheet (MSN)

The synthesis of MSN was realized simply with one inlet flow containing diluted TEOS in ethanol (0.18 M) and the other CTAB (0.01 M) and TBAI (0.01 M) in diluted ammonia (0.03 M).

The two inlet flows were pumped (Pump 33 DDS, Harvard Apparatus) into the spiral microchannel at flow rates of 25 µL/min and 200 µL/min, respectively. The as-synthesized products were collected at the outlet. After washing several times with water and ethanol, the product was undertaken calcination treatment (gradient heating from r.t. to 600 °C, 8 hours). The obtained white solid was then stored in a dry place for further analysis.

2.4 COMSOL simulation and theoretical analysis

Firstly, Reynolds number (Re) was calculated to determine if the fluids are in laminar flow regimes: $Re = \rho UL/\mu$, where the density ($\rho \sim 1000 \text{ kg/m}^3$) and dynamic viscosity ($\mu \sim 0.001 \text{ Pa}\cdot\text{s}$) of water are used for approximations, L is the characteristic length, and U is the average flow velocity, which could be obtained by: $U = \frac{\text{flow rate}}{W \cdot H}$. In our case with the spiral microchannel, $W = 500 \text{ }\mu\text{m}$, $H = 50 \text{ }\mu\text{m}$, when flow rate is at 1000 µL/min, $U = 0.675 \text{ m/s}$, and $Re = 15.15 < \sim 2300$. When the flow rate of 200 µL/min or less is used, the Re will be even smaller.

Therefore, the fluids are in laminar flow. We consider them as incompressible with no-slip boundary condition and neglect the gravity force for simplicity. The flow rates for two inlets are 25 and 200 µL/min, respectively. The outlet is set to be fixed pressure with $p = 0$. The diffusion coefficient used is $D = 5 \times 10^{-10} \text{ m}^2/\text{s}$, which is the value normally used for the mixing of water and ethanol.

2.5 Calculation of the time for the synthesis of MSN via microfluidic device

In this study, the width and height of the microchannel are 500 µm and 50 µm, respectively. The spiral-shaped microchannel is made of three arcs with the diameters of 7.69 mm, 13.8 mm, and 22.2 mm, with the central angles of 180°, 180°, and 225°, respectively. To estimate the time for synthesis, firstly, the length of the channel is calculated, which is 7.73 cm. Then the volume of fluids in the channel is calculated to be 1.93 µL. Thus, with a flow rate of 200 µL/min, the time for the synthesis of nanosheet structure is $\sim 0.58 \text{ s}$.

2.6 Tunable synthesis of mesoporous silica products

To examine the specific roles of CTAB, TBAI, ammonia, TEOS, and flow rates of inlets, a series of control tests were carried out. For all these tests, only one parameter was changed while others were kept constant.

2.7 Investigation of the enrichment capacity of MSN by optical microscopy

To investigate the enrichment capacity of MSN by optical microscopy, all materials including adsorbent (MSN) and adsorbate (RB, BSA, and Dox) were prepared at the same concentration of 0.1 mg/mL. After pumping two fluids through the two-run microfluidic channel at the same flow rate of 100 μ L/min under dark condition, several drops of the fluid from the outlet were collected and spread onto the glass slide surface immediately. Then, the glass slides were examined under an Olympus BX51. To compare the color difference before and after enrichment, MSN was treated same as above.

2.8 Qualitative and Quantitative measurement of the enrichment performance of RB by MSN

To qualitatively and quantitatively measure the enrichment performance of RB by MSN, two fluids, MSN (0.1 mg/mL as adsorbent) and RB (0.1 mg/mL as adsorbate), were pumped through the two-run microchannel under dark condition. The flow rate of RB was kept at 100 μ L/min and the flow rates of MSN were chosen as 10, 20, 50, 100, 200, 500, and 1000 μ L/min. For qualitative measurement by fluorescent microscopy, several drops of the fluid from the outlet were collected and spread onto the glass slide surface immediately. The fluorescent images were taken by Olympus BX51 using the same exposure time. For quantitative measurement by UV-VIS spectroscopy, after centrifugation of the fluid collected from the outlet, the remaining amount of RB in the supernatant was determined using UV-VIS Spectrophotometer (SHIMADZU Corporation) based on the standard calibration curve of RB at 554 nm. Quantitative measurement results were obtained in triplicates.

2.9 Qualitative and Quantitative measurement of the enrichment performance of BSA by MSN

Qualitative and Quantitative measurement of the enrichment performance of BSA was similar as the treatment protocol of RB. We used BSA-FITC conjugate for qualitative measurement by fluorescent microscopy, but for quantitative measurement by UV-vis spectroscopy, we used BSA for better simulating the interactions between MSN and protein.

2.10 Qualitative and Quantitative measurement of the enrichment performance of Dox by MSN

Qualitative and Quantitative measurement of the enrichment performance of Dox was similar as the treatment protocol of RB. The drug loading amount was determined by UV-vis spectroscopy at 233 nm using a standard calibration curve of Dox.

2.11 Characterization

Transmission electron microscopy (TEM) was performed on a Tecnai F20ST field emission gun (FEG) transmission electron microscope operating at an accelerating voltage of 200 kV.

Scanning electron microscopy (SEM) was performed on a XL-30 field emission gun environmental scanning electron microscope. Nitrogen adsorption–desorption measurements were carried out to determine the textural properties of silica materials by using a Quantachrome NOVA 4200e surface area analyzer at $-196\text{ }^{\circ}\text{C}$. The prepared products were dried at $150\text{ }^{\circ}\text{C}$ before analysis. Pore-size distributions were estimated from adsorption branches of the isotherms by using the Barrett–Joyner–Halenda (BJH) method. Pore volumes were determined from the amounts of N_2 adsorbed at the single point of $P/P_0 = 0.98$. The powder X-ray diffraction (XRD) data were obtained by a Bruker D8 focus diffractometer.

3. Results and discussion

Microfluidic flow and continuous synthesis of two-dimensional MSN was realized in the miniaturized two-run spiral-shaped microreactor with two inlets and one outlet (Figure 2A). The microfluidic device was fabricated using soft lithography. Briefly, after obtaining the master mold, the polydimethylsiloxane (PDMS) precursor was poured over it, left to solidify and peeled off to get the replica. Then the PDMS replica was treated with oxygen plasma and bonded to the glass slide to form microchannels (Figure 2B). The spiral-shaped microchannel is made of three arcs with the diameters of 7.69 mm, 13.8 mm, and 22.2 mm, with the central angles of 180° , 180° , and 225° , respectively. The width and the height of the microchannel are $500\text{ }\mu\text{m}$ and $50\text{ }\mu\text{m}$, respectively. The two inlet reactant flows, one containing diluted TEOS in ethanol (0.18 M) at a flow rate of $25\text{ }\mu\text{L}/\text{min}$ and the other containing CTAB (0.01 M) and TBAI (0.01 M) in diluted ammonia (0.03 M) at a flow rate of $200\text{ }\mu\text{L}/\text{min}$, were pumped (Pump 33 DDS, Harvard Apparatus) into the spiral-shaped microreactor at room temperature and the MSN product was collected at the outlet. Owing to the transverse Dean flow effect,^[17,18] the spiral-shaped microreactor is expected to achieve rapid and intensive mixing.^[19,20] As revealed by COMSOL analysis, complete mixing can be achieved within one-run (Figure 2C).

Given the merits from microreactors, especially the rapid and intensive mixing, we expect that the desired nanostructures could be continuously produced quickly over a short flow distance within the microchannel (less than 8 cm in length). When the flow rates of TEOS and CTAB/TBAI inlet fluids were set as 25 and $200\text{ }\mu\text{L}/\text{min}$, respectively, white colloidal particles can be obtained within 0.6 s from the outlet of microreactor. As shown in figure 3A, well-defined silica nanosheet structure can be clearly observed under SEM. These nanosheets have an average diameter of ca. $15\text{ }\mu\text{m}$ and an average thickness of ca. 100 nm . A majority of them exhibit circular disk-like morphology. From the high magnification SEM images (Figures 3B–C), it is noted that silica nanosheet surface shows well-ordered water ripple-like wrinkles. These wrinkles form regular ridges on the nanosheet surface, and the ridges are nearly parallel to each other (Figure 3D). The ridge width of the water ripple-like pattern is ca. 50 nm with an interval of ca. 50 nm between the two ridges (Figure 3D). Observations from TEM images not only confirmed the water ripple-like pattern of the as-synthesized silica nanosheet material (Figures 3E–G), but also revealed the presence of abundant mesopores distributed into the silica matrix (Figure 3H). Nitrogen sorption analysis was further performed on the resultant mesoporous silica nanosheet (MSN) after calcination treatment for removing the organic moieties. The results showed that MSN

exhibits a typical type IV isotherm with H3 hysteresis (Figure S1A), indicating the presence of slit-shaped and large-sized pores.^[21,22] The Barrett–Joyner–Halenda (BJH) pore size, Brunauer–Emmett–Teller (BET) surface area, and pore volume were measured to be 3.1 nm, 904.8 m²/g, and 0.89 cm³/g, respectively (Figure S1). Wide-angle X-ray diffraction analysis for MSN further revealed its amorphous structure (Figure S2).

According to the above-mentioned observations, the obtained two-dimensional silica nanosheet not only exhibits abundant mesopores but also displays unique water ripple-like wrinkles on its surface (Figure 4, left panel). It is noted that, besides these easily recognizable properties, more clues from SEM showed that MSN should have more complicated hollow sandwich-like architectures (Figure 4, middle and right panels). Broken MSN particles in SEM images (Figures 4 and 5A) revealed that MSN is obviously composed of two solid layers and a hollow cavity between them. The external of two solid layers of MSN shows water ripple-like rough surface, whereas, the internal is relatively smooth surface. The presence of hollow cavity in MSN is in good agreement of multiple and wide pore size distributions from nitrogen sorption analysis (Figure S1B).

To explore the formation mechanism of two-dimensional MSN with hollow sandwich-like bilayer structure and water ripple-like wrinkle surface, we examined the specific roles of CTAB, TBAI, ammonia, TEOS, and flow rates of inlets. In the absence of TBAI, only micrometer scale spherical particles were obtained (Figure 5B), whereas, there were no well-defined particles formed without the addition of CTAB. Decreasing the concentration of CTAB/TBAI would obtain a mixture of nanosheets with plain surface and spherical nanoparticles (Figure 5C), while increasing it would produce irregular thick fibers (Figure 5D). These results suggest that CTAB and TBAI act as the structure-directing agent and structure-stabilizing agent, respectively, during the formation of the scaffolds of MSN. Decreasing and increasing the concentration of ammonia obtained nanosized irregular particles (Figure 5E) and nanosheet with plain surface (Figure 5F), respectively, indicating the important role of ammonia as catalyst for the catalytic hydrolysis of TEOS and the formation of two-dimensional silica structure. The thickness of the nanosheet is changed as a function of TEOS concentration (Figures 5G and 5H), showing the primary role of TEOS in silica matrix formation and growth. In addition, by tuning the flow rates of inlet fluids, the concentrations of chemical reactants were changed correspondingly, which will further affect the properties of the resultant materials. For example, when increasing the flow rate of TEOS fluid, thick nanosheet structures can be also obtained, but there is no water ripple-like pattern on particle external surface (Figure 5I), which is similar as the product prepared by increasing the concentration of TEOS (Figure 5H). Based on these investigations, a cooperative assembly mechanism was proposed for elucidating the formation of two-dimensional hollow sandwich-like MSN with water ripple-like surface (Figure 6). Through the classical liquid crystal templating approach,^[1,23] these two cationic surfactants, CTAB and TBAI, are self-organized into two-dimensional multilayer lamellar arrangement micelles.^[24] When two inlet fluids meet at the interface, favored by the energy gained by decreasing the surface tension, CTAB and TBAI micelles will form a bilayered skeleton;^[22,25] meanwhile, these micelles will also coalesce to form a multilamellar phase at the interface (Figure 6, Step I).^[24,26] The confined silica precursor, TEOS, by the supramolecular templates of two cationic surfactants (CTAB and TBAI) will then hydrolyze

and deposit on micellar surface via electrostatic attractions to form mesophase structures (Figure 6, Step II).^[1,27] Due to the continuous cocondensation of TEOS and the hydrodynamic interactions between micellar vesicles,^[25,28] the cooperative dual templates will finally evolve into the building blocks of MSN and form unique two-dimensional hollow sandwich-like bilayer structure and water ripple-like wrinkle surface (Figure 6, Step III).

Owing to its unique multilevel porous structure, water ripple-like coarse surface, and hollow sandwich-like bilayer, MSN may greatly improve particulate accessibility toward different substrates and expand its use as host materials. In combination with the aforementioned merits of microfluidics such as rapid and intensive mixing, MSN may exhibit superior on-chip enrichment performance for mass transfer. To demonstrate this, we examined the enrichment behavior of MSN as adsorbent on three different adsorbates, Rhodamine B (RB, an organic dye), bovine albumin (BSA, FITC conjugate for visualization) and doxorubicin hydrochloride (Dox, an anticancer drug), through the two-run microfluidic platform. The effect of inlet flow rates on the enrichment capacity of MSN was firstly investigated. According to the COMSOL simulation results, when keeping the flow rate of adsorbate fluid constant at 100 $\mu\text{L}/\text{min}$ and changing the flow rates of adsorbent fluid from 10 to 1000 $\mu\text{L}/\text{min}$, two fluids can achieve complete mixing with two runs or less (Figure 7A). The bigger difference of the inlet flow rates, the more rapid mixing performance of adsorbate and adsorbent. It is noted that, in all the cases above, the residence time (*i.e.*, enrichment time of adsorbent to adsorbate) only ranges from 0.116 to 1.16 s. Optical images showed that, after flowing both adsorbent (MSN, 0.1 mg/mL) fluid and adsorbate (RB, BSA, or Dox, 0.1 mg/mL) fluid at a flow rate of 100 $\mu\text{L}/\text{min}$, the resultant particles exhibit typical light pink, cyan, and red color for RB-enriched MSN, BSA-enriched MSN, and Dox-enriched MSN, respectively, suggesting the greatly rapid on-chip enrichment performance of MSN (Figure 7B). By the aid of the specific fluorescence and optical absorption characteristics of RB, BSA, and Dox, we then qualitatively and quantitatively measure the enrichment capacity of MSN by fluorescent microscopy and ultraviolet–visible spectroscopy, respectively (Figures 7C–E). Fluorescent results showed that MSN could efficiently enrich RB (red), BSA (green), and Dox (red) at a relatively broad flow rate ratio (R) of adsorbate fluid to adsorbent fluid, and brighter fluorescence could be observed with higher R value. Quantitative results further revealed that dye adsorption rates (Figures 7C and S3), protein immobilization rates (Figures 7D and S4), and drug encapsulation rates (Figures 7E and S5) by MSN were obviously R -dependent, which agree well with the COMSOL simulation results from figure 7A. The lower the R value (*i.e.*, the larger amount of adsorbent), the higher the enrichment rates. In addition, MSN showed obvious higher enrichment capacity of RB and Dox than that of BSA in all R cases, probably because of its relatively large size dimension.^[29] At the highest R value (100:10), the maximum on-chip enrichment amount of RB, BSA, and Dox can achieve 1.24, 0.55, and 0.93 gram per gram of MSN, respectively, which were significantly higher than those of silica sphere synthesized from microreactor under the same conditions (Figure S6). Considering the rapid interaction time (second-scale or less) and high throughput, such microfluidic on-chip enrichment platform could endow MSN with promising potential in organics adsorption, protein immobilization, and drug encapsulation,

especially when compared to conventional low-efficiency hour- or day- scale treatment of mesoporous silica materials in these fields (Table S1).

4. Conclusions

In summary, using a spiral-shaped microfluidic device, we first developed a facile and straightforward flow synthesis strategy to create two-dimensional nanosheet and examined its on-chip enrichment performance toward different substrates. The resultant mesoporous nanosheet that was obtained from one inlet flow containing TEOS and the other CTAB and TBAI in diluted ammonia exhibited typical hollow sandwich-like bilayer structure and unique water ripple-like wrinkle surface. The formation mechanism of MSN was explored by investigating the effect of chemical reagents concentration and flow rates on the structural properties. Given its inherent advanced morphology, MSN showed greatly enhanced particulate accessibility for mass transfer. Theoretical analysis and experimental investigations demonstrated the rapid and efficient on-chip enrichment capacity of MSN for RB adsorption, BSA immobilization, and Dox encapsulation. These findings not only provide new insights for the rational design and controllable synthesis of functional micro-/nanomaterials through microreactors, but also open up numerous new possibilities by microfluidic platforms for applications like organics adsorption, protein immobilization, and drug encapsulation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Microfluidic formation and on-chip enrichment application of two-dimensional mesoporous silica nanosheet.

Figure 2.

(A) Photograph of the two-run microreactor with a U.S. quarter dollar for scale. The microfluidic channel was filled with a blue dye for visualization. (B) Fabrication procedure of two-run spiral microfluidic device. (C) COMSOL simulation result of mixing in the microfluidic channel when the flow rates of TEOS and CTAB/TBAI were set as 25 and 200 $\mu\text{L}/\text{min}$, respectively.

Figure 3. Scanning electron microscopy (SEM) images (A–D) and transmission electron microscopy (TEM) images (E–H) of as-synthesized mesoporous silica nanosheet with unique water ripple-like surface. The inset in figure B shows a water ripple drawing.

Figure 4. Schematic drawing (top panel) of the top view, perspective view, and cross-section view of the hollow sandwich-like mesoporous silica nanosheet with unique water ripple-like surface and the corresponding representative SEM images (bottom panel). Objects are not drawn to scale.

Figure 5.

Tunable synthesis of mesoporous silica products. (A) SEM image of broken MSNs showing the water ripple-like external surface and smooth internal surface. (B-I) SEM images of the product prepared using the same protocol as MSN except for without the addition of TBAI (B), or decreasing the concentration of CTAB and TBAI from 10 mM to 2.5 mM (C), or increasing the concentration of CTAB and TBAI from 10 mM to 40 mM (D), or decreasing the concentration of ammonia from 30 mM to 7.5 mM (E), or increasing the concentration of ammonia from 30 mM to 120 mM (F), or decreasing the concentration of TEOS from 180 mM to 45 mM (G), or increasing the concentration of TEOS from 180 mM to 720 mM (H), or increasing the flow rate of TEOS fluid from 25 $\mu\text{L}/\text{min}$ to 100 $\mu\text{L}/\text{min}$ (I).

Figure 6.

Proposed formation mechanism of two-dimensional hollow sandwich-like MSN with water ripple-like surface. The process undergoes three phases, *i.e.*, self-assembly of CTAB and TBAI (step **I**), hydrolysis of TEOS (step **II**), and cocondensation of silicates (step **III**). Objects are not drawn to scale.

Figure 7.

(A) COMSOL simulation results of mixing at different flow rate ratios of adsorbate to adsorbent. From the top to the bottom panels are shown respectively for 100:10 (i), 100:20 (ii), 100:50 (iii), 100:100 (iv), 100:200 (v), 100:500 (vi), and 100:1000 (vii) at $\mu\text{L}/\text{min}$ level. (B) Optical images of MSN (i), RB-enriched MSN (ii), BSA-enriched MSN (iii), and Dox-enriched MSN (iv) when the flow rates of both inlet fluids were set as 100 $\mu\text{L}/\text{min}$. Scale bar=20 μm . (C), (D), and (E) are the enrichment performance of MSN as a function of flow rate ratio toward RB, BSA, and Dox, respectively. The insets are the corresponding

representative fluorescent images of MSN after enrichment tests. Each set of images was acquired with the same exposure time.

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