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Phosphate modulated permeability of mesoporous silica sphere: a biomimetic ion channel decorated compartment model

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Due to its high loading capacity, permeability modulation, and biological compatibility, mesoporous silica sphere provides a suitable system for mimicking the cellular compartments. Herein, surface amine group functionalized mesoporous silica sphere was developed as a biomimetic compartment model, in which the ion permeability can be well modulated through the external phosphate ion. The amine group was selectively modified on the surface of the mesoporous silica sphere in the presence of template molecule (CTAB) in the mesochannel. The surface amine group was employed as a gatekeeper shell and the specific binding of anionic phosphate with the amine groups reversed the surface charge from positive to negative and gated the permeability of the model cationic $Ru(bipy)_3^{2+}$. Ion channel decorated compartment is one of the key architectual principles of the cell, which maintains a high local reagent concentration inside via the high surface area interior, and whose permeability is tuned by a collection of ligand gated ion channels outside to ensure metabolism balance. The permeability modualtion in mesoporous silica sphere closely resembles that observed in biological ion channel decorated compartment in vivo. This protocol opens the possibility of simulating the process of ion permeability in biological compartment based on mesoporous silica sphere and it will also contribute to the design of artificial cell and bio-inspired responsive nanoreactors.

Introduction

The design and operation of artificial systems with similar structure and function as cellular compartments constitutes a fascinating challenge in the field of biology, materials science, catalysis, biotechnology and biomedicine, for it will expand our understanding of the biological compartmentalization and build biomimetic highly functional structures.[1-6] So far, biomimetic compartments have been developed based on phospholipid and surfactant vesicles,[7, 8] polymersomes,[9-11] colloidosomes,[12-15] proteinosome,[16-18] and membrane-free micro-droplets.[19-21] It has been utilized to mimic one or more key aspects of their biological counterparts, such as enzyme-mediated transformations,[22] RNA catalysis,[23] cell-free gene expression.[21, 24] An ideal biomimetic compartment should compose of a structurally robust and biocompatible core-shell structure: an interior core to accommodate and concentrate guest molecules for highly efficient internalized chemical transformations, and a stimulus-responsive and semi-permeable external shell, which modulates the permeation of nutrients and wastes. Lipid, fatty acid and amphiphilic block copolymer vesicles have been used to build artificial compartments.[7, 22, 25] However, as these kinds of compartments suffer from low permeability and in order to enhance the membrane permeability, several natural and synthetic pore-forming molecules are usually utilized to insert, which are always expensive and difficult to handle.[8, 26] Mann and co-workers used silica nanoparticles with a balance of hydrophilic and hydrophobic surface properties to fabricate a biomimetic nanoparticle enclosed compartment with a number of nanopores connecting the inner and outer space of the compartment. The permeability was highly improved as the guest molecules can permeate through the nanopores freely.[13] pH responsive permeability was also achieved via functionalization of a zwitterionic copolymer. Despite of such advances, it is still desirable to develop biomimetic compartments with robust core-nanoporous shell structure and more stimulus-responsive gating performance.

Mesoporous silica spheres have attracted much attention for its large pore volume, high surface area and tunable pore size from 2 to 50 nm.[27-29] It defines a nanoconfined inside which has been used to accommodate drug and enzymes.[30-35] The confined inside is also regarded as an ideal space for catalytic reaction because of its large surface area and spatial localization.[36-40] In our previous work,[41] we found that the permeation of ionic species into mesoporous silica nanospheres depends on the electrostatic interaction between the charged guest molecule and the channel wall. Permselectivity was realized as a result of electrical double layer overlap in the narrow channels and it can also be modulated

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via the solution pH and ion strength. In order to construct a biomimetic ligand gated compartment, functional groups with gating properties are needed as a gatekeeper shell for responsive permeation modulation.

In this work, inspired by the architecture of ion channel decorated compartment in biological system, a biomimetic phosphate gated compartment was constructed via amine group functionalization on the outer surface of mesoporous silica sphere. The surface amine group acted as a gatekeeper shell to control the permeation of guest molecule into the biomimetic compartment. By employing the specific interaction between phosphate and amine group, phosphate gated permeation of cationic $Ru(Bipy)_3^{2+}$ into the biomimetic compartment was achieved. It was demonstrated that the specific binding of phosphate ion changed the surface charge of the mesoporous silica sphere from positive to negative, which changed the interaction for the cationic guest molecule from repulsion to attraction. The protocol shows the potential of mesoporous materials as basic element to build biomimetic compartment and it will contribute to the design of artificial cell and responsive nanoreactor based on mesoporous materials.

Experimental section

Materials

N-cetyltrimethylammonium bromide (CTAB, ~99%) was purchased from Alfa Aesar. Tetraethylorthosilicate (TEOS, 28%) and sodium hydroxide (NaOH) were purchased from Xilong reagent company (Guangdong, China). 3-Aminopropyltris (methoxyethoxyethoxy) silane (APTMEES) was purchased from Gelest. $[Ru(bipy)_3]Cl_2$ (bipy =2,2′ -bipyridine) dye ($Ru(bipy)_3^{2+}$) were purchased from Sigma-Aldrich. Disodium phosphate ($Na_2HPO_4 \cdot 12H_2O$), sodium sulfate (Na_2SO_4), sodium chloride (NaCl), sodium nitrate ($NaNO_3$), sodium acetate trihydrate ($NaAc \cdot 3H_2O$) and potassium bromide (KBr) were purchased from Sinopharm Chemical Reagent Co., Ltd (Shanghai China). All salt solutions were prepared with ultrapure Milli-Q water (Resistance >18.2 MΩ.cm).

Characterization

Transmission electron microscopy (TEM) images were obtained on a FEI Tecnai G2 F20 TEM at a 200 kV accelerate voltage. UV−vis spectra were carried out on a UV-vis 1601 Shimadzu spectrophotometer. Small angle powder X-ray diffraction patterns of the MSS-NH_2 materials were obtained in a Scintag XDS-2000 powder diffractometer, using Cu Kα irradiation (λ = 0.154 nm). N_2 adsorption−desorption isotherms were obtained at −196 °C on a Micromeritics ASAP 2010 sorptometer by static adsorption procedures. Samples were degassed at 100 °C and 10^{-3} Torr for a minimum of 12 h prior to analysis. Fourier transform infrared (FTIR) spectra were obtained from a TENSOR 27 spectrometer, Bruker Instruments Inc., Germany. The zeta potentials of the mesoporous silica spheres under different salt of different concentration were measured at 25 °C using a Malvern Nano ZS90 laser particle analyzer.

Preparation of surface amine functionalized mesoporous silica nanospheres

First, mesoporous silica spheres were synthesized with the template molecule CTAB by the following procedures:[42] 0.50 g CTAB was dissolved in 240 mL of nanopure water. Then, 1.75 mL NaOH aqueous solution (2.0 M) was introduced to the CTAB solution and the temperature of the mixture was adjusted to 85 °C. Subsequently, 2.5 mL TEOS (11.2 mmol) was added dropwise to the surfactant solution under vigorous stirring. The mixture was then allowed to react for 2 h to give rise to a white precipitate. Finally, this solid crude product was filtered, washed with nanopure water and methanol. The product was dried under high vacuum at 60 °C to yield the as-synthesized MSS-OH (CTAB) (hydroxyl functionalized mesoporous silica sphere with CTAB in the channels).

Then, surface amine functionalization of mesoporous silica nanosphere was performed in the presence of CTAB in the mesochannels.[43] 0.4 g as-made MSS-OH (CTAB) was suspended in anhydrous toluene (80 ml), and 0.2 ml APTMEES was added to the mixture. The solution was refluxed for 24 h. It was cooled down to room temperature, and the product was centrifuged, washed thoroughly with methanol. The product was then dried under high vacuum and the white powder was named MSS-NH_2 (CTAB) (surface amine functionalized mesoporous silica sphere with CTAB in the channels). To remove the surfactant template CTAB, the MSS-OH (CTAB) and the MSS-NH_2 (CTAB) were suspended in a mixture of 2 mL of HCl (37%) and 36 mL of methanol, and the solution was heated twice under reflux for 12 h. The resulting material was filtered and extensively washed with nanopure water and methanol. The resulting products were then placed under high vacuum to remove the remaining solvent in the mesochannels. The samples were donated as MSS-OH (hydroxyl functionalized mesoporous silica sphere) and MSS-NH_2 (surface amine functinalized mesoporous silica sphere).

Permeability of surface amine functionalized mesoporous silica spheres

The permeability comparison of MSS-OH and MSS-NH_2 was first performed. 5 mg MSS-OH and 5 mg MSS-NH_2 were added respectively into 1.0 mL aqueous solutions of $Ru(bipy)_3^{2+}$ (5 mM) in water. The mixtures were sonicated for 30 s and then incubated in a Thermostated Mixing Block (MB-102, Bioer) for 24 h, at 25 °C, operating at 1300 rpm. The suspensions were separated by centrifugation prior to analysis of the supernatant and their UV-vis adsorption spectra were recorded. For the permeation of MSS-NH_2 in different concentrations of phosphate, 5 mg MSS-NH_2 was added respectively into 1.0 mL aqueous solutions of $Ru(bipy)_3^{2+}$ with different concentrations of phosphate from 0 mM to 10 mM (pH 8.0). The permeation comparison with different common anions was performed in 5 mM of Na_2SO_4, NaCl, $NaNO_3$, NaAc and KBr. After incubation continued for 24 h, the suspensions were separated by centrifugation prior to analysis of the supernatant by detecting the absorbance at 454 nm. Standard curves were generated for $Ru(bipy)_3^{2+}$ over appropriate concentration range for the samples to determine the permeation amount.

Results and discussion

Principle

Due to its high loading capacity, permeability modulation, and

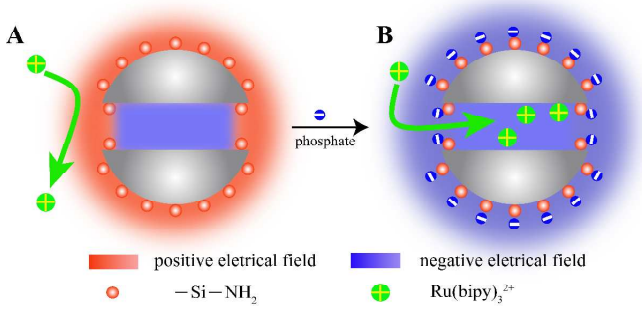

Figure 1. Protocol for biomimetic phosphate gated compartment. The surface amine groups on the mesoporous silica sphere can be taken as a gatekeeper shell. (A) In the absence of phosphate, the permeation of $Ru(bipy)_3^{2+}$ will be hindered as a result of the electrostatic repulsion of the positively charged surface amine group. (B) In the presence of phosphate, the permeation would be opened as the surface charge will be reversed from positive to negative as a result of the specific binding between the anionic phosphate and amine groups.

biological compatibility, mesoporous silica sphere can be considered as a suitable candidate for biomimetic cellular compartment construction. The large pore volume inside will provide sufficient space for chemical or biological process to take place and the local reactant concentration would be enhanced substantially because of the high surface area of the channel wall. The ion channel-like surface nanopores will render the particle high permeability and the permeation can be modulated via convenient functionalization of the silica nanopores. Moreover, the silica mesostructure is robust and thermal stable in different environment. Herein, we used mesoporous silica nanoparticle as a basic material to build a biomimetic phosphate gated compartment (Figure 1). Amine group was functionalized selectively on the surface of the particle as a gatekeeper shell to modulate the permeation of guest molecules. Due to the distribution of negatively charged –Si-OH groups inside the particle and its weak binding with amine group, cationic $Ru(bipy)_3^{2+}$ was chosen as model guest molecule for the permeation research as it size is estimated to be 1.2 nm,[44] which confirmed that it is small enough to enter the host mesoporous nanochannels. Though the cationic $Ru(bipy)_3^{2+}$ preferentially resides in the negatively charged and high surface area compartment interior, the permeation would be hindered by the nanoporous amine group shell. As in the gatekeeper shell, when the salt concentration is low, the electrical double-layer in the nanochannels would overlap, which results in the repulsion of molecules of the same charge into the pore.[41] Thus, in the absence of phosphate, the permeation of $Ru(bipy)_3^{2+}$ will be hindered. However, in the presence of phosphate, the permeation would be opened as the surface charge will be reversed from positive to negative as a result of the specific binding between the anionic phosphate and the amine groups. The situation closely resembles that observed in biological ion channel decorated compartment in vivo, in which the permeation of guest molecule into the compartment interior through ion channels are modulated by the binding of ligands.

Synthesis and characterization of surface amine group functionalized mesoporous silica sphere

The surface amine group functionalized mesoporous silica sphere was synthesized in a two step procedure. First, mesoporous silica sphere was synthesized with CTAB as template molecule. Then, APTMEES was grafted on the surfactant filled mesoporous silica sphere, in which the surfactant filled pores can hinder the entry of APTMEES and permit selective functionalization on the outer surface of the particles.[45] The functionalization process was characterized by FTIR (Figure 2A). Before the surface grafting step, MSS-OH (CTAB) displayed the absorption at 1080, 798, and 468 cm^{-1}, which were assigned to the asymmetric stretching, symmetric stretching, and bending of Si−O−Si vibration respectively, and the broad absorption band at 3450 cm^{-1} was attributed to the stretching of the Si−OH group. The strong absorption band at 2923 cm^{-1}, 2854 cm^{-1} and 1475 cm^{-1} were assigned to the carbon chain and the tertiary amine of CTAB respectively. After functionalization of APTMEES, the peaks for CTAB stayed the same while a new peak assigned to N–H asymmetric bending vibration appeared at 1555 cm^{-1}, which confirmed the successful functionalization of amine groups. The

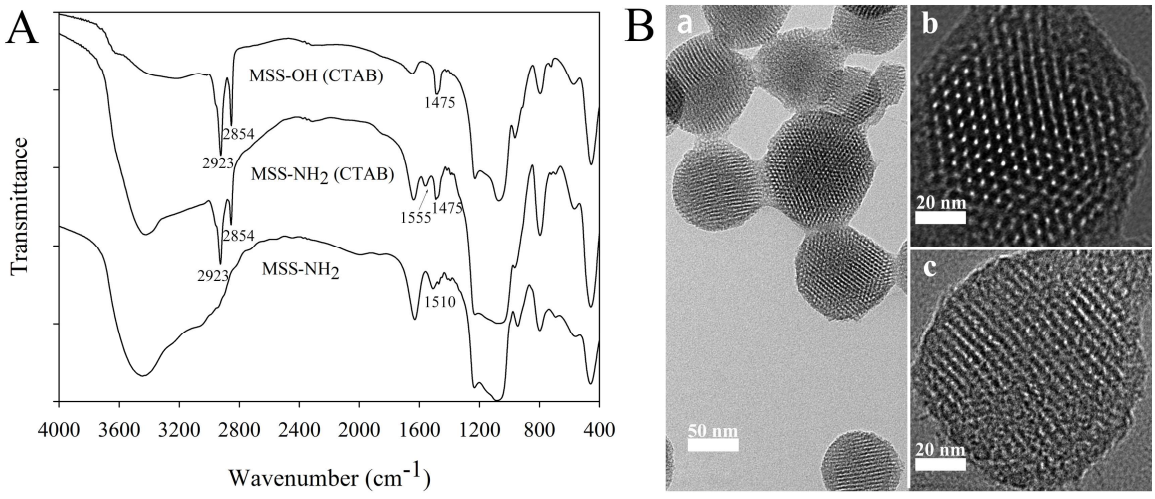

Figure 2. (A) FTIR of MSS-OH (CTAB), MSS-NH_2 (CTAB) and MSS-NH_2. (B) TEM of MSS-NH_2

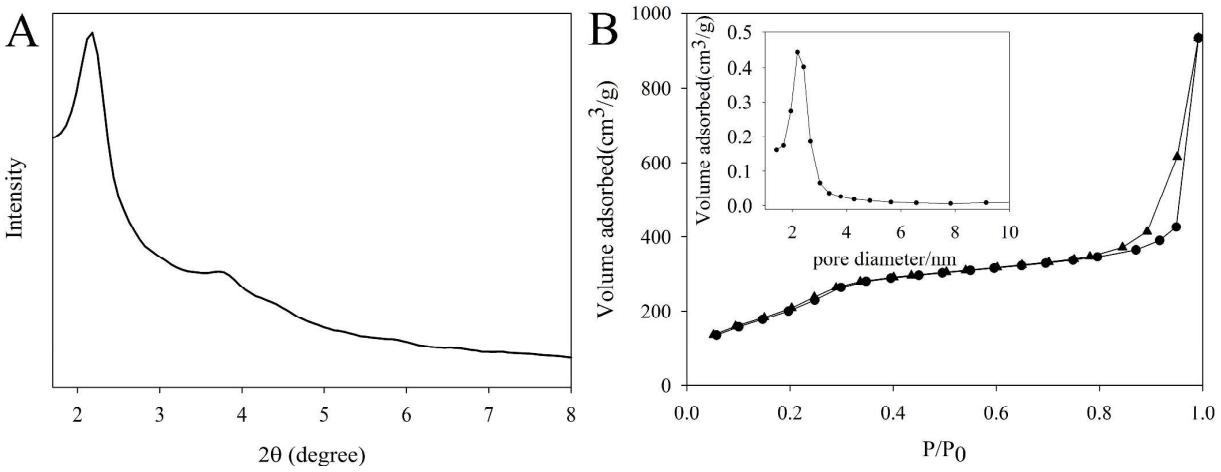

Figure 3 (A) XRD of MSS-NH_2. (B) Sorption isotherms and the pore size distribution (inset) of MSS-NH_2.

results indicated that the template molecule CTAB was still confined in the pore and the amine groups were presumably mainly anchored on the particle surface. After the template removal step in ethanol solution of hydrochloric acid, the adsorption band of CTAB disappeared and the peak of amine group shifted from 1555 cm^{-1} to 1510 cm^{-1} as a result of protonation.[43, 46] The FTIR results validated the successful preparation of MSS-NH_2 and completely removal of template molecule. The morphology and pore architecture of the product were then characterized. Figure 2B shows TEM images of the as-prepared MSS-NH_2, which possessed a monodispersed spherical morphology with an average diameter of about 86 nm. As shown in the HRTEM image in Figure 2B (b), the particle surface was coated with high density of nanopores, which had the size of about 2.2 nm and were highly orderly distributed. While in the interior of the particle, as shown in Figure 2B (c), highly ordered parallel nanochannels of about 2.2 nm could be observed. The mesostructure was also confirmed by powder X-ray diffraction (XRD) pattern (Figure 3A). The as-prepared MSS-NH_2 exhibited a definite diffraction peak at 2.1 (2θ) with a shoulder peak around 3.8 , which can be indexed as (100), (110) Bragg peaks of a hexagonal ordered array, suggesting perfect long-range order in this material. The N_2 adsorption-desorption isotherms showed that the pore volume and the surface area of the nanospheres was 1.506 cc/g and 979.218 m^2/g, and the average pore diameter was 2.188 nm with a narrow pore distribution (Figure 3B). Thus, surface amine functionalized mesoporous silica sphere was successfully synthesized. Biological compartments always possess ion channels around, which maintains a high local reagent concentration inside via the high surface area interior, and whose permeability is tuned by a collection of ligand gated ion channels outside to ensure metabolism balance. The synthesized surface amine functionalized mesoporous core-shell structure closely resembles ion channel decorated compartment in vivo. The surface nanopores can be regarded as ion channel analogue which connect the environment and the inner channels can be regarded as cytoskeleton analogue which provide sufficient sites for chemical or biological process to take place.

Permeability of amine group functionalized mesoporous silica sphere as a biomimetic compartment

The permeability of the amine group functionalized mesoporous silica sphere was then investigated. The permeation of $Ru(bipy)_3^{2+}$ was performed in the absence and presence of amine shell on the mesoporous silica sphere: MSS-OH and MSS-NH_2. The permeation experiments were performed in aqueous solution of 0.02 mM $Ru(bipy)_3^{2+}$ and the permeation amount was estimated from the UV-vis adsorption change of the guest molecule in the supernate fluid after centrifugation. For the solution containing MSS-OH, almost all the $Ru(bipy)_3^{2+}$ molecules in solution permeated into the particle, as the adsorption of the supernate fluid at 454 nm approached zero and the sedimented particles were deep yellow colored (Figure 4). It indicated the accumulation ability of the mesoporous silica sphere for the cationic guest molecule which resulted from the electrostatic attraction, large volume and high surface area inside. While for the permeability of the surface amine functionalized biomimetic compartment, $Ru(bipy)_3^{2+}$ did not permeate into the particles at all for the adsorption spectrum of the supernate fluid nearly overlapped that of the mother solution and the sedimented particles were white colored. In the presence of surface amine groups around the particles, the positively charged amine groups electrostatically rejected the cation molecule, even with a great

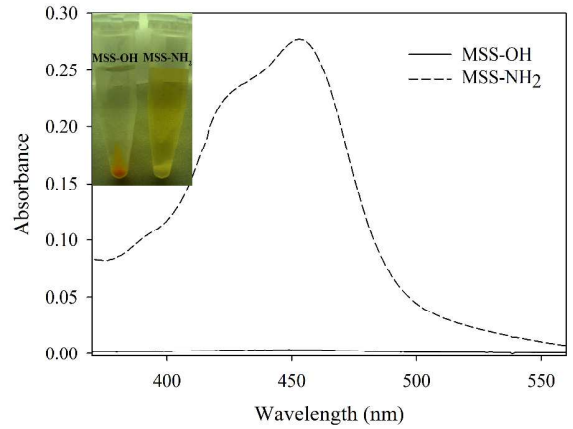

Figure 4. UV-vis adsorption spectra of the $Ru(bipy)_3^{2+}$ supernatant after incubation with MSS-OH and MSS-NH_2. Inset: the corresponding photographs.

deal of negatively charged Si-OH groups in the interior of the particle. It was also verified by the zeta potential of MSS-OH and MSS-NH_2, -20.8 mV and 34.6 mV respectively.

The surface amine functionalized mesoporous silica sphere, having an interior of high loading ability, and a nanoporous gatekeeper shell of amine groups on the particle surface, which resemble biological ion channel decorated compartments. In order to biomimic the gating performance of biological ion channel decorated compartments, i.e., modulate the permeation of cationic guest molecules into the biomimetic compartment, a negatively charged amine-binding ligand is needed for the the permeation of cationic guest molecules into the particle.

Phosphate gated permeability of amine group functionalized mesoporous silica sphere

Amine group has been extensively used as suitable groups for the design of receptors to bind anionic guests.[47] Due to its strong interaction with amine,[47, 48] phosphate was chosen as a potential ligand for gating the biomimetic amine enclosed compartment. For the phosphate gating experiment, $Ru(bipy)_3^{2+}$ was added into the solution of as-prepared MSS-NH_2 in the presence of phosphate at different concentration (from 0 mM to 10 mM, pH 8.0). The permeation of $Ru(bipy)_3^{2+}$ into the biomimetic compartment was calculated from the concentration change of guest molecule in the supernate fluid after centrifugation. As shown in Figure 5A, the permeation amount of $Ru(bipy)_3^{2+}$ in MSS-NH_2 increased gradually as the concentration of phosphate increased. The permeation amount of $Ru(bipy)_3^{2+}$ reached 0.5 μmol/g at 5 mM phosphate and did not change obviously above 5 mM. The results showed that phosphate can clearly gated the permeation of $Ru(bipy)_3^{2+}$ into the biomimetic compartment. As the cation was hindered via electrostatic rejection, the charge state of the compartment in the presence of phosphate was investigated. The zeta potential of MSS-NH_2 in different concentration of phosphate (Figure 5B) showed that the binding of phosphate with the particle surface quite changed the surface charge. As the concentration of phosphate increased, the zeta potential of the particle decreased from +34 mV to about 0 mV at 1 mM, and then turned negatively charged as the concentration increased continuously and reached plateau after 5 mM. The charge state change was in accordance with that of permeation amount. As reported in our previous work, for the permeation of charged species in mesoporous silica nanoparticles, the electrostatic interaction between the guest molecule and the mesochannel wall is the primary factor that dominates the permeation process. Though the inner part of the MSS-NH_2 possessed Si-OH groups negatively charged in the pH range which was in favor with cationic $Ru(bipy)_3^{2+}$ permeation, the surface anchored amine groups was positively charged and form a positively charged electrical field. Due to the nanometer size of

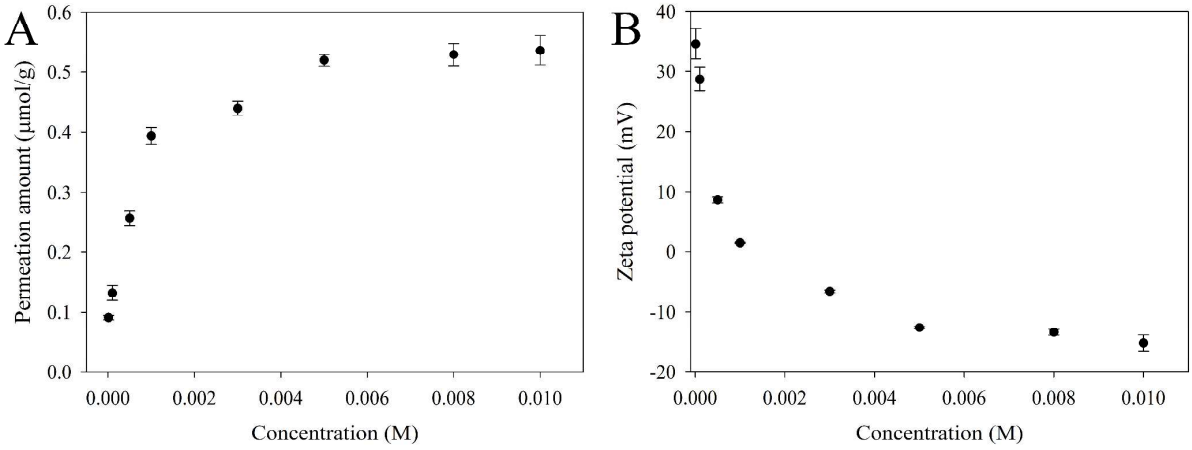

Figure 5. (A) Permeation of $Ru(bipy)_3^{2+}$ in MSS-NH_2 in different concentration of phosphate solution. (B) Zeta potential of MSS-NH_2 in different concentration of phosphate solution.

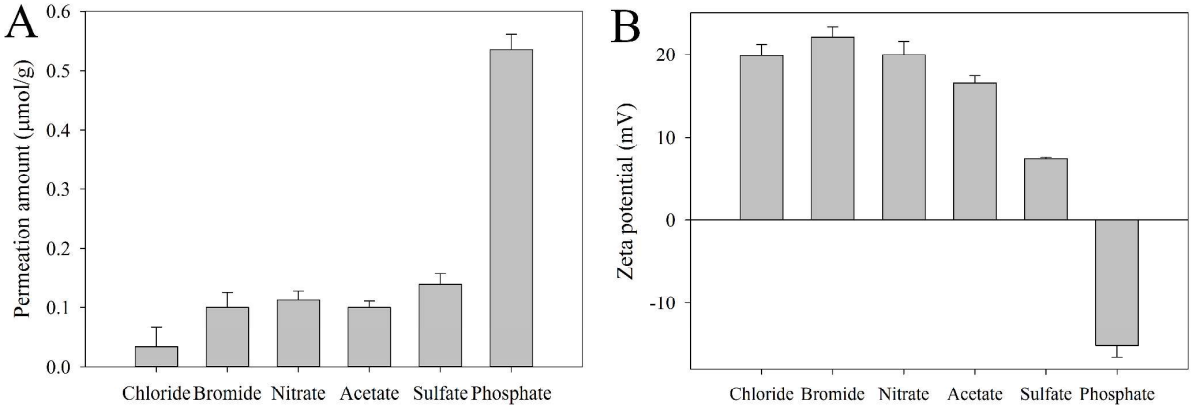

Figure 6. (A) Permeation of $Ru(bipy)_3^{2+}$ in MSS-NH_2 in different anions solutions (5 mM). (B) Zeta potential of MSS-NH_2 in different anions solutions (5 mM).

the surface pores, the electrical double layers of the pore wall overlapped and only permit the permeation of substance having charge opposite to the porous surface.[41] Thus, the access of the cationic guest molecules was hindered, which resulted in the low permeation of $Ru(bipy)_3^{2+}$. While in the presence of phosphate, the charge state was neutralized and reversed because of the highly negatively charged phosphate and its strong hydrogen bonding with amine groups on the surface.[49] The charge reversal turned the electrostatic rejection to attraction for the cationic guest molecule and enhanced the permeation of $Ru(bipy)_3^{2+}$ to a large extent. In order to investigate the specificity of the gating performance, the permeation and zeta potential in other anions were investigated. As shown in Figure 6, compared with other common anions, only phosphate reversed the zeta potential of the particle and the permeation amount was much higher than that in solution of other anions. Thus, a biomimetic phosphate gated compartment based on MSS-NH_2 was successfully constructed via the electrostatic interaction modulation between the guest molecule and the surface nanoporous ligand binding amine groups shell.

Conclusions

In summary, taking the advantage of high loading capacity, permeability modulation, and biological compatibility of mesoporous silica materials, we have constructed a biomimetic phosphate gated compartment based on inhomogeneous functionalization of mesoporous silica sphere, for it has the similar features of nanoporous surface with uniform nanopores, large pore volume and high surface area inside as biological compartment. The phosphate gated permeation was achieved via the specific binding of phosphate with the nonporous surface-anchored amine groups, which reversed the surface charge and gated the access into the biomimetic compartment. Compared with other biomimetic compartments, the model has the following advantages: the inherent ion channel-like nanoporous surface and cytoskeleton-like nanochannels inside, the ease of functional group modification of the inner and outer surface of the silica structure, larger mechanical and colloidal stability, as well as the biological compatibility of mesoporous silica materials. We reason that by changing the size of the channel and surface functional groups, this biomimetic compartment can accommodate many kinds of substances, such as ion, drug and protein. The protocol opens the possibility of developing new biomimetic mesoporous silica compartments for artificial cell and responsive nanoreactor. Perspectively, further efforts would be focused on the direction of more ligand gated permeation and biochemical reaction modulation in the biomimetic compartment.

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Table of Content

Surface amine group functionalized mesoporous silica sphere was developed as a biomimetic compartment model, in which the ion permeability can be well modulated through the external phosphate ion. This protocol opens the possibility of simulating the process of ion permeability in biological compartment based on mesoporous silica sphere.