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Composite microparticles of halloysite clay nanotubes bound by calcium carbonate

Yi Jin [a,*], Raghuvara Yendluri [b], Bin Chen [a], Jingbo Wang [a], Yuri Lvov [b,c,*]

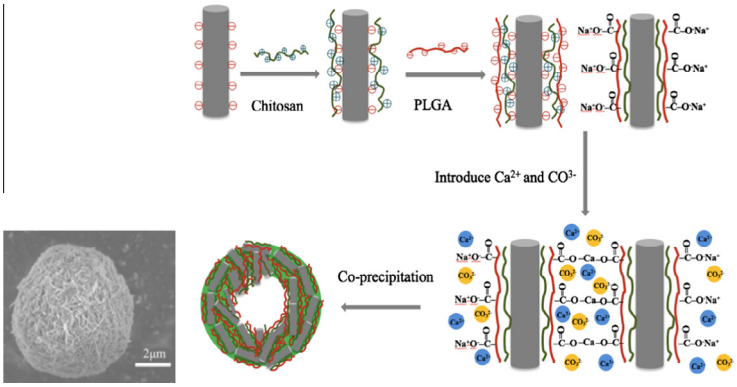
[a] Institute of Chemical Engineering, Ningbo University of Technology, Ningbo 315016, China
[b] Institute for Micromanufacturing, Louisiana Tech University, Ruston, Louisiana 71272, USA
[c] Ural Federal University, Ekaterinburg 620002, Russia

HIGHLIGHTS

- Halloysite nanotubes were modified with chitosan and alginate by LbL self-assembly.
- $CaCO_3$–HNT microspheres prepared by Ca^{2+} alginate binding followed by CO_2 bubbling.
- The composite particles were non-toxic and biocompatible.
- The composites are empty spheres with abundant pore distributions and higher surface area.
- The slow sustained release of nifedipine from the nanocomposite was achieved.

GRAPHICAL ABSTRACT

A layer-by layer assembly technique was used to accomplish halloysite clay nanotube alginate binding with Ca^{2+} followed by CO_2 bubbling to prepare nanotube-calcium carbonate composite spheres. These composite particles have abundant pore distribution range of 2.5–13 nm and surface area of 82 m^2 g^{-1}.



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ABSTRACT

Natural halloysite clay nanotubes with 15 nm inner and 75 nm outer diameters have been used as vehicles for sustained release of drugs in composite hollow microparticles "glued" with $CaCO_3$. We used a layer-by layer assembly accomplished alginate binding with Ca^{2+} followed by CO_2 bubbling to prepare the composite microspheres of $CaCO_3$ and polyelectrolytes (PE) modified halloysite nanotubes (HNTs–PE_2/$CaCO_3$) with the diameter of about 5–10 μm. These microparticles have empty spherical structure and abundant pore distributions with maxima at 2.5, 3.9, 6.0 and 13.3 nm, and higher surface area of 82.3 m^2 g^{-1} as characterized by SEM and BET test. We loaded drugs in these micro-nano carriers of tight piles of halloysite nanotube with end clogged with $CaCO_3$. The sustained release of Nifedipine drug from HNTs–PE_2/$CaCO_3$ composite microspheres was slower than for pristine halloysite nanotubes.

1. Introduction

Halloysite nanotubes (HNTs) are a naturally available clay mineral with external diameter of 50–75 nm, lumen of 10–15 nm and length of about 1000 nm [1–3]. Its inner surface consists of a

* Corresponding authors at: Institute for Micromanufacturing, Louisiana Tech University, Ruston, Louisiana 71272, USA. Tel.: +1 318 257 5144; fax: +1 318 257 5104 (Y. Lvov). Tel.: +86 138 0587 4816; fax: +86 0574 8708 1240 (Y. Jin).
E-mail addresses: jinyimail@163.com (Y. Jin), ylvov@latech.edu (Y. Lvov).

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gibbsite octahedral sheet (Al–OH) groups with positive electrical potential, whereas the external surface is composed of siloxane groups (Si–O–Si) with negative surface charge [4–10]. Halloysite has been proved to be environmental friendly and biocompatible which enables it to be a promising nanomaterial for developing organic/inorganic composites for control release in the biomedicine field including drugs, enzymes and DNA delivery [11–16]. With 15 nm lumen consisting ca 15 vol.% of the nanotubes, usage of halloysite nanocontainers for loading and sustained release of functional chemicals seems to be the most remarkable for applications. The in vitro release characteristics of different drugs from halloysite show sustained release with typical time period of 5–20 h [3]. The drug-halloysite release curves give a bust release 50–60% of the load in the first 1–2 h with slowing release in the following time. We assume that clogging the nanotube ends (making a kind of end-stoppers) would allow further slowing down the release kinetics. Therefore, a complexation of clay nanotube with biocompatible calcium carbonate looks as a promising strategy for developing nano-micro vehicles for controlled drug delivery.

Vaterite $CaCO_3$ spherical particles with the diameter of 3–5 μm are composed of nanocrystals bound to each other as fibrous aggregates thus forming channel-like structure with a pore size in the range of 20–40 nm [17,18]. They have been useful decomposable cores for templating bioactive molecules ether by formulation of microbeads with the biomolecules such as proteins or by encapsulation of the biomolecules into the layer-by-layer formed LbL-multilayer capsules [19–24]. For its nontoxic, highly surface area and mild decomposition conditions the vaterite $CaCO_3$ particles were used for drug release systems [25–28]. Recently, Parakhonskiy et al. prepared $CaCO_3$ particles whose geometry was controlled by varying optimizing speed, time, and pH value of the reaction solution, and ratio of the interacting salts. These microparticles were used for studying uptake by living cell and appeared to be an attractive drug delivery platform [29].

Considering high potential of these two of biocompatible nano-micro materials for controlled release, new HNTs–PE_2/$CaCO_3$ composite microspheres were designed. We used a layer by layer assembly accomplished with alginate binding with Ca^{2+} followed by CO_2 bubbling to prepare the hollow microspheres of $CaCO_3$ and halloysite nanotubes (HNTs/$CaCO_3$) with the diameter of about 5–10 μm. This nano-micro composite has several advantages: both of the components are none or low toxic, and are highly porous but with different pore size and internal pore chemistry (positive and negative), which can be loaded with drugs. Nifedipine is a dihydropyridine calcium channel blocker that primarily blocks L-type calcium channels [30]. Its main uses are as an antianginal and antihypertensive. It is also commonly used for the small subset of pulmonary hypertension patients whose symptoms respond to calcium channel blockers. We loaded nifedipine in the pristine halloysite nanotubes and porous HNTs/$CaCO_3$ nano-micro composites to optimize the drug releasing profile.

2. Experiment sections

2.1. Materials

The raw halloysite was supplied from Henan Province, China. All other chemicals and drugs were purchased from Sigma–Aldrich and used without further purification. Chitosan (CH) (Mw ~ 100 kDa) and sodium polyalginic acid (PLGA) were used as polycation and polyanion for LbL assembly with their sequential adsorption. Calcium chloride dehydrate ($CaCl_2$), sodium carbonate (Na_2CO_3) were used for synthesis of calcium chloride microspheres. Nifedipine was used for loading and releasing study. The water used was purified with a three-stage Millipore Milli-Q Plus 185 system.

2.2. Formation of nanoshells on halloysite tubes with layer-by-layer (LbL) method

The negatively charged halloysite (60 mg) was incubated with 20 mL chitosan-CH solution containing 1 wt.% acetic acid and 0.5 Mol/L NaCl for 30 min, followed by three centrifugation (5000 rpm, 5 min) washing cycles with 1 wt.% acetic acid solution. At the second step, the CH-coated halloysite was added into 20 mL alginate – PLGA solution containing 0.5 Mol/L NaCl; 30 min was allowed for adsorption, and three centrifugation/washing cycles were performed. The cationic chitosan and anionic alginate adsorption steps were repeated to build two bilayer shell on the clay nanotubes. The assembly process was monitored with zeta-potential measurements using Zeta Plus, Brookhaven Instruments Corp.

2.3. Synthesis of HNT–PE_2/$CaCO_3$ microspheres

Co-precipitation reaction of two salts is a typical method to prepare vaterite $CaCO_3$ microcores, and introducing protein or other chemicals into these particles [31–34]. This method was used to prepare the HNTs–PE_2/$CaCO_3$ composite microspheres (Scheme 1). PE_2-means two polycation/polyanion bilayer shell. First, halloysite was coated with LbL chitosan/alginate shell, then CO_2 was bubbled 20 min into this dispersion, followed by addition of 5 mL 0.5 M $CaCl_2$ and bubbling for another 30 min. The final composite nano-micro spheres were washed in water three times and dried at 60 °C.

To compare with the nanoshelled halloysite composite HNT–PE_2/$CaCO_3$, we also prepared the bare pristine halloysite HNT/$CaCO_3$ composites via co-precipitation. The HNT was dispersed in 10 mL 0.5 M $CaCl_2$ solution, then CO_2 was bubbled into the halloysite dispersion for 30 min. The obtained composite microspheres were washed by water and dried at 60 °C.

2.4. The loading and releasing experiments

Saturated solution of nifedipine was prepared by dissolving 20 mg of the drug in 1 mL of ethanol. 50 mg of HNTs or 50 mg of HNTs–PE_2/$CaCO_3$ composites was added to the above solution. The mixture is dispersed and sonicated for 5–10 min to form a homogeneous dispersion. The dispersion is placed in a vacuum chamber for 30 min for three cycles followed by overnight vacuuming. The samples are washed twice with ethanol by centrifuging at 8000 rpm for 3 min and dried in a vacuum dessicator. The loading efficiency was determined using TGA.

For release control the drug-loaded halloysite and composite nano-micro spheres were placed into 10 mL of phosphate buffers (pH 7.4) at 37 °C with stirring. At suitable intervals, 1 mL of the dissolution medium was taken for testing. The equivalent volumes of fresh medium were added. The concentration of nifedipine was determined at 236 nm using UV/VIS Agilent Techn. Spectrophotometer.

2.5. Characterization

Hitachi scanning electron microscopy (SEM, HITACS S-4800) and transmission electron microscopy (Tecnai G2 F30 Twin, USA) were used to characterize the morphology of halloysite and composite particles. X-ray studies were performed with Bruker-D8 Discover XRD instrument, the scan rate was 0.5° $(2\theta)\,min^{-1}$ with a step size of 0.02°. Thermogravimetric analysis (TGA) was performed under nitrogen flows from room temperature to 1000 °C at a heating rate of 20 °C/min using a DuPont 1090B Thermal Analyzer. BET was conducted with nitrogen porosity meter NOVA 2200e, Quatachrome Instrument Inc.