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Poly (vinylsulfonic acid) assisted synthesis of aqueous solution stable vaterite calcium carbonate nanoparticles

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ABSTRACT

Calcium carbonate nanoparticles of the vaterite polymorph were synthesized by combining $CaCl_2$ and Na_2CO_3 in the presence of poly (vinylsulfonic acid) (PVSA). By studying the important experimental parameters we found that controlling PVSA concentration, reaction temperature, and order of reagent addition the particle size, monodispersity, and surface charge can be controlled. By increasing PVSA concentration or by decreasing temperature CCNPs with an average size from ≈150 to 500 nm could be produced. We believe the incorporation of PVSA into the reaction plays a dual role to (1) slow down the nucleation rate by sequestering calcium and to (2) stabilize the resulting CCNPs as the vaterite polymorph, preventing surface calcification or aggregation into microparticles. The obtained vaterite nanoparticles were found to maintain their crystal structure and surface charge after storage in aqueous buffer for at least 5 months. The aqueous stable vaterite nanoparticles could be a useful platform for the encapsulation of a large variety of biomolecules for drug delivery or as a sacrificial template toward capsule formation for biosensor applications.

1. Introduction

Calcium carbonate is an important material for fundamental and applied study, with implications in industrial [1], household [2], and biological processes [3]. Calcium carbonate exists as three different anhydrous polymorphs: calcite, aragonite and vaterite in order of increasing solubility and decreasing thermodynamic stability. Nanoporous calcium carbonate particles have attracted much attention because of their biocompatibility, high effective surface area, ability to protect encapsulated components, larger pore size than mesoporous silica, inexpensive production under ambient conditions, and ease of dissolution with mild treatment of EDTA at neutral pH [4]. There is significant interest in producing the vaterite polymorph of calcium carbonate because it has better water solubility, higher porosity, and is more easily dissolved than calcite or aragonite. However, the thermodynamic instability of vaterite makes its natural occurrence rare, requiring kinetic stabilization even for laboratory production. Investigation into different crystal growth modifiers for vaterite formation is encompassed by the vast literature studying additive-directed crystallization [5,6], for its importance in understanding mesocrystal formation for biomineralization [7,8]. It is difficult to predict the outcome of different additives from theory; hence, most understanding is gained through empirical observations. Additional factors such as concentration and ratio of Ca^{2+} to CO_3^{2-}, temperature, pH, reaction duration, and mixing speed all influence the outcome and further complicate understanding the process. Polymers act to inhibit or stabilize specific crystal structures, reshaping and directing crystal formation depending on chemical composition, charge density, and concentration [9]. A wide variety of structures and crystal polymorphs can be produced, with even a small amount of additive having a significant influence on the outcome. Copolymers containing both interacting and stabilizing components reshape crystallization based on the affinity of the chemical structure for the mineral salt ions and crystal faces [10]. In recent work, the commercial random copolymer poly (4-styrenesulfonate-co-maleic acid) (PSS-co-MA) was found to direct crystallization to produce a variety of superstructures depending on its relative concentration to calcium in the reaction [8,11]. A PEI assisted ultrasonic method was developed for the synthesis of vaterite microparticles that were stable for at least 8 months [12]. Other commonly used polyelectrolytes used include carboxylic or sulfate containing synthetic and biopolymers [13,14].

Abbreviations: PVSA, poly (vinylsulfonic acid); CCNP, calcium carbonate nanoparticle; DLS, dynamic light scattering; NTA, nanoparticle tracking analysis; BET, Brunauer–Emmett–Teller.

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For biosensor or drug delivery applications the production of spherical vaterite is desired because the highly porous structure can serve as a template for biomolecule incorporation. Encapsulation into these particles is achieved either by adsorption to the highly porous structure after particle formation [15] or by addition during nucleation to coprecipitate during particle formation [16]. In many cases, the biomolecule-encapsulating calcium carbonate microparticle is used as a template to create hollow capsules by the sequential deposition of oppositely charged polyelectrolytes using electrostatic layer-by-layer, followed by core dissolution [17]. Applications of calcium carbonate nanoparticles (CCNPs) would have vast implications for both drug delivery and sensor applications. In order for a drug-carrying nanoparticle to passively enter a subcutaneous tumor cell it must be less than the 200–1200 nm pore size cutoff [18]. For competitive binding glucose biosensors, compartmentalization of macromolecules into nanocapsules should improve response times by decreasing diffusion distances [19].

Production of CCNPs requires decreasing the particle growth rate and stabilizing the NPs before they agglomerate to form microparticles or recrystallize to calcite. Alginate chains have been used to reduce the nucleation growth rate by sequestering calcium, resulting in the formation of CCNPs [20]. However, the resulting CCNPs showed an increase in size and loss of negative surface charge after 4 h in aqueous solution, indicating surface recrystallization. Ethylene glycol was used to reduce the solubility and crystal growth rate of calcium carbonate to produce vaterite nanoparticles down to 430 nm in size [21]. These particles remained as vaterite in ethanol, but recrystallized to calcite when transferred to aqueous solutions. Thus, while a few examples of efforts to produce CCNPs have been reported, we have not identified any that yield long-term aqueous stable vaterite nanoparticles.

The focus of this work was to study the effect of poly (vinylsulfonic acid) (PVSA) on CCNP formation and production of vaterite nanoparticles. It has been shown that the presence of sulfonic groups on polymers stabilizes the vaterite structure [2]. We hypothesized that incorporation of commercially available PVSA, a low-molecular-weight and high-charge-density polyelectrolyte, would limit interparticle bridging and aggregation of primary nuclei to prevent microparticle formation. This idea was based on a previous report of the copolymer of PVSA and chitosan which found that the sulfonate groups strongly interacted with and attached to the calcium carbonate surface [22]. Here we describe a method to obtain vaterite CCNPs and report how PVSA concentration, reaction temperature, and order of reagent addition affect particle size, morphology, surface charge, and crystalline structure.

2. Experimental section

2.1. Chemicals

PVSA (Sigma) was filtered through a 0.2 μM syringe filter prior to use. Na_2CO_3 and $CaCl_2$ (Sigma) was used as received. PVSA molecular weight of 4000–6000 kDa according to manufacturer's specifications, 5000 kDa was used for calculations.

2.2. CCNP synthesis

About 10 ml of 20 mM Na_2CO_3 and PVSA were added to a 100 ml beaker and stirred at 800 RPM with a spinning wedge stir bar (VWR). After 1 min, 10 ml of 20 mM $CaCl_2$ was rapidly injected. The beaker was covered and the solution was allowed to react at RT for 1–14 h depending on the PVSA concentration (Table S1). The mixture was transferred to 50 ml conical tube and centrifuged at 10,000 g for 5 min to recover the formed particles and remove unreacted components. The particles were washed 3 times with 50 mM pH 9 Tris buffer and finally resuspended as a 1 ml stock solution in 50 mM pH 9 Tris buffer. This process was also done in reverse where $CaCl_2$ was added first followed by PVSA and then Na_2CO_3 (Table S2).

2.3. Scanning electron microscopy (SEM)

Images were obtained with a JEOL FE-SEM 7500. 2 μl of a 1/10 diluted stock dilution was placed on a cleaned silica support and dried in a vacuum chamber overnight followed by gold sputtering for 45 s.

2.4. XRD

The X-ray source was a 2.2 kW Cu X-ray tube, maintained at an operating current of 40 kV and 40 mA. The standard Bragg–Brentano para-focusing mode with the X-ray diverging from a DS slit (1 mm) at the tube to strike the sample and then converging at a position sensitive X-ray Detector (Lynx-Eye, Bruker-AXS). The two-circle 250 mm diameter goniometer was computer controlled with independent stepper motors and optical encoders for the θ and 2θ circles with the smallest angular step size of $0.0001°2\theta$. Data collection was automated COMMANDER program by employing a DQL file and was analyzed by the program EVA.

2.5. DLS and ζ-potential

Dynamic Light Scattering (DLS) and ζ-potential was measured using a Zeta Sizer Nano Series ZEN 3600 Spectrometer (Malvern Instruments Ltd., Malvern, Worcestershire, United Kingdom). A 1 ml, 1/20 diluted stock solution in 5 mM pH 9.0 Tris buffer was used for measurement.

2.6. Nanoparticle tracking analysis (NTA)

Particle size and distributions were obtained with the NanoSight LM10HS with a 65 mW 405 nm source. A 300 μl sample of a 1/100 dilution of the sample stock solution in 0.1 M bicarbonate buffer was used for analysis. Video was acquired with a Hamamatsu C11440 digital camera for 3 min in order to obtain at least 1000 particle tracking events. Analysis was completed with included NanoSight 2.3 software with automatic settings.

2.7. UV–VIS spectroscopy

UV–VIS absorbance was obtained on a Cary 300 UV–VIS spectrophotometer with a 6×6 multi-cell peltier block and temperature controller. For the time dependent studies a scaled down reaction in a 3 ml total volume (1.5 ml $CaCl_2$, 1.5 ml Na_2CO_3, and PVSA) was monitored at 500 nm at 20–30 s intervals under constant stirring.

2.8. Brunauer–Emmett–Teller (BET) method

The surface area and pore size of the $CaCO_3$ nanoparticles was determined using the BET method with nitrogen adsorption and desorption at 77 K using a Micromeritics ASAP 2000.

3. Results

The simple experimental setup is depicted in Scheme 1 where equal volumes of equimolar of $CaCl_2$ and Na_2CO_3 are combined under agitation in the presence of PVSA. In the first set of experiments 10 mLs of 0.02 M Na_2CO_3 was combined with PVSA in a beaker and