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Original Research Paper

Ultrasonically assisted fabrication of vaterite submicron-sized carriers

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ABSTRACT

Ultrasonically accomplished precipitation of calcium carbonate was demonstrated as a novel beneficial method for the formation of porous submicron vaterite particles with low dispersity, high mass yield, and the "scaling up" possibility. The effect of sonication on the size and crystallographic phase of formed particles was investigated by comparing this method with a magnetic stirring and non-stirring interfusion. By virtue of their porosity, vaterite particles allow the different substance incorporation. The loading properties of synthesized particles were demonstrated for high molecular weight substance (labeled protein), as well as for low molecular one (fluorescent dye). Such features open up perspectives of drug encapsulation and delivery for the vaterite submicron carriers.

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1. Introduction

Nanomedicine, and especially design of novel containers for drug delivery, is an intensively developing area. Created container should meet such requirements, as efficient substance loading, biocompatibility, storage property, while providing an address delivery and *in situ* release at a certain time in a right dose. Furthermore, a successful method of the delivery system fabrication should be reproducible and manufacturable, that is adaptable to industrial production. Regarding these criteria, porous inorganic micro- and nanoparticles offer high stability, providing at the same time necessary upload capacities and release rates for the specific substance. One of this type of materials is calcium carbonate based structures.

In the last decade, natural or synthesized calcium carbonate has been widely used in tissue engineering, for cartilage repair [1], especially for bone repair, where carbonate scaffolds advantageously substitute bone grafts by providing the 3D support [2]. Calcium carbonate is biodegradable material and has an excellent cytocompatibility, either alone [3] or in a combination with other materials [4–6].

Calcium carbonate presents the phenomenon of polymorphism having at least three anhydrous polymorphs: calcite with rhombohedral lattice and cubic appearance, aragonite – whiskers like crystals with orthorhombic lattice and vaterite with hexagonal lattice and spherical appearance [7].

Vaterite is the least thermodynamically stable polymorph of $CaCO_3$. It represents a polycrystalline with quite large surface area and negative zeta potential. These properties as well as biocompatibility and high cell uptake efficiency [8,9] make the vaterite particles perspective as smart containers for various personal care and biomedical applications [10], especially for drug encapsulation [11–18], as templates for the formation of microcapsules [19–22], hydroxyapatite [23], or osteogenic devices for bone regeneration [24], or as synthetic bone substitutes [25]. Moreover, being unstable and pH-sensitive, vaterite particles hold out the prospect of a novel biodegradable drug delivery system [26,27]. Vaterite particles can be a part of composite materials: with Ag or Au nanoparticles for enhanced Raman signal [23,28], Fe_3O_4 for manipulated by external magnetic field [29] or clay nanotube for providing additional encapsulation release efficiency [30].

There are two principal chemical methods of $CaCO_3$ synthesis: solid-state and wet synthesis. A solid-state displacement reaction occurs during mechanical milling of the reaction powder mixture. However this method is suitable just for formation of the particles with irregular shape and size distribution, thus has limited applicability. Meanwhile wet chemical methods based on the precipitation of $CaCO_3$ crystals from the reaction solution, which contains calcium and carbonate ions, have lots of realization ways

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allowing the size control and quality improvements of obtaining particles by variation of physical and technological parameters of the synthesis [31].

In the last years, effective methods for controlling the size from 430 nm [32] to 5 μm [19] of vaterite particles were developed. Variation of the salts ration during the calcium carbonate synthesis opened up the possibility of star-like and elliptic particles formation in the same size range [21,33].

Homogeneous mixing of the reaction solution ensures the uniform distribution of the growth centers and leads to formation of uniform particles. The known methods of vaterite synthesis generally cannot provide the formation of particles with a narrow size distribution. Besides, scale up of the reaction volume in an effort to increase the amount of synthesizing calcium carbonate gets some "quality" (uniformity, porosity, etc.) loss of the sample being a result of hydrodynamic processes in the reaction mixture. Thus, for example, while mixing with a magnetic stirrer, a stirring speed [34], features of the glass surface, a shape and a size of the stir bar [35] as well, as it's position in the glass [36], have an influence on properties of obtained particles.

To solve the problems described above, in current work we suggested the usage of ultrasonic agitation during the calcium carbonate synthesis. Variation of the ultrasonic power and field dynamic [37], can help to control the course of precipitation and crystallization processes [38,39]. Sonication of a liquid medium is a driving force for mass transfer and can initiate cavitation. Cavitation bubble implodes forming the localized hot spot with high temperature and high pressure releasing a powerful shock wave and liquid microjets [40]. Both influences as results of cavitation bubble collapse affect on a primary nucleation during the crystallization process increasing a nucleation rate and reducing the aggregation of growth centers, that decreases the crystal size and it's distribution and accelerates the crystal precipitation [41]. The influence of the power and time of US-treatment on a size of aragonite crystals [42], calcite particles [43], primary calcium carbonate seeds [44–46] were investigated. Few notification of US-assisted formation of vaterite particles have demonstrated, that the particles had a large size (more than 2 μm) dispersity and nonuniform shape [45,47,48].

In present work we focused on the effect of sonication during the calcium carbonate synthesis on the size, dispersity, crystallographic phase of formed particles and $CaCO_3$ mass yield. Furthermore, the "scaling up" possibility for the synthesis was studied. To show the proof of principle of drug encapsulation, the loading properties of the vaterite carriers were studied for bovine serum albumin labeled with tetramethylrhodamineisothiocyanate (Mw ≈ 66 kDa), as for model high molecular weight substance, and for Rhodamine 6G (Mw = 0.479 kDa), as for model substance with a low molecular weight.

2. Experimental section

2.1. Materials

Sodium carbonate (Na_2CO_3), calcium chloride ($CaCl_2$), red-fluorescing tetramethylrhodamineisothiocyanate–bovine serum albumin (TRITC–BSA) and Rhodamine 6G (Rho6G) were purchased from Sigma–Aldrich and used without any additional purification. Deionized water produced with a water treatment system MF-1812F-6 (RPC Mediana-Filter, Russia) was used in all experimental stages.

2.2. Preparation of calcium carbonate particles

Calcium carbonate particles were fabricated using different techniques based on the previously reported protocol [19]: equal volumes of 0.33 M Na_2CO_3 and 0.33 M $CaCl_2$ water solutions were quickly poured into a glass vessel at room temperature. To investigate the effect of mixing method on the size and shape of obtaining particles, three different manipulations were done: the reaction solution was agitated during 90 s under sonication by the ultrasonic homogenizer Sonopuls (Bandelin, Germany) at the frequency of 20 kHz and power density of 1 W/cm^2 ("US agitation" at Fig. 1c) or was mixed using the magnetic stirrer Mini MR Standart (IKA, Germany) at 500 rpm ("stirring with magnetic bar" at Fig. 1b), or, as a control, was left without mixing for 90 s ("control" at Fig. 1a). The synthesized $CaCO_3$ particles were thoroughly washed with water and ethanol and dried for 30 min at 60 °C.

To investigate the effect of volume of the reaction mixture, all synthesis were done in two different reaction mixture volumes: "small" – equaled to 7.5 ml (3.75 ml of 0.33 M Na_2CO_3 added to 3.75 ml of 0.33 M $CaCl_2$) and "large" volume equaled to 60 ml (30 ml of 0.33 M Na_2CO_3 added to 30 ml of 0.33 M $CaCl_2$).

2.3. Characterization techniques

Particle morphology characterization was performed by the scanning electron microscopy (SEM) with MIRA II LMU device (Tescan) at the operating voltage of 20 kV, magnification was ranged from 100 to 40,000 times. Samples were prepared by drying of a drop of the microparticle suspension on a silicon wafer.

Size distribution and polydispersity index of the calcium carbonate particles was obtained by post processing and image analysis of SEM micrographs (see supporting information) with Image J software (NIH, http://rsb.info.nih.gov/ij/). At least 300 measurements per sample were performed.

X-ray diffraction patterns of powders were obtained on Xcalibur/Gemini and PDS120 (Nonius GmbH, Solingen) diffractometer using Cu Kα radiation. The accelerating voltage and the applied current were 40 kV and 40 mA, respectively. The theoretical $CaCO_3$ spectra were taken from the works of Sitepu [49] and Le Bail et al. [50] for calcite and vaterite, respectively.

The specific surface area of calcium carbonate particles was evaluated using NOVA 1200e analyzer (Quantachrome, United

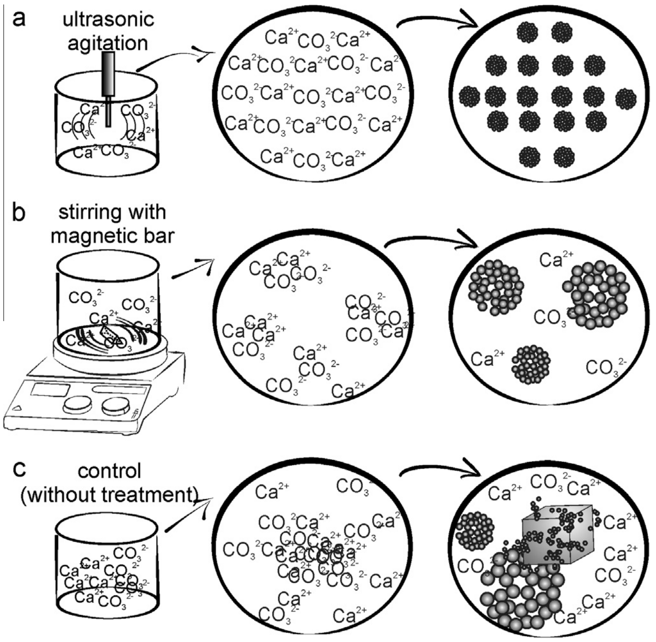

Fig. 1. Schematic of particle formation under different treatments: panel a – control experiment (without any treatment), panel b – stirring with a magnetic bar, and ultrasonic agitation – panel c.

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