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Incorporation of negatively charged iron oxide nanoparticles in the shell of anionic surfactant-stabilized microbubbles: The effect of NaCl concentration

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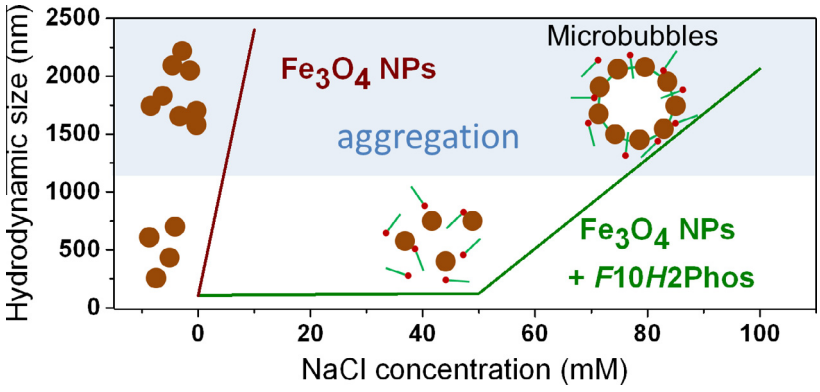
HIGHLIGHTS

- Stabilization of magnetic iron oxide nanoparticle-decorated microbubbles at pH 11.
- Flocculation of the NP suspension to stabilize the microbubbles.
- Hollow microspheres with solid shells of 100–200 nm in thickness.

GRAPHICAL ABSTRACT



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ABSTRACT

We report on the key effect of NaCl for the stabilization of nanoparticle-decorated microbubbles coated by an anionic perfluoroalkylated phosphate $C_{10}F_{21}(CH_2)_2OP(O)(OH)_2$ surfactant and negatively charged iron oxide nanoparticles. We show that hollow microspheres with shells of 100–200 nm in thickness can be stabilized even at high pH when a strong ionic force is required to screen the negative charges. Due to the more drastic conditions required to stabilize the hollow microspheres, they appear to be stable enough to be deposited on a surface and dried. That can be a simple way to fabricate porous ceramics.

1. Introduction

Increasing attention is being paid to air microbubbles in numerous scientific and technological areas [1,2]. In medicine, microbubbles are a unique ultrasound-triggered platform allowing the combination of imaging and drug delivery for theranostic

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applications [3–5]. Several commercial products containing microbubbles are currently available for diagnostic procedures in the cardiovascular field [6]. They are mainly bubbles with polymeric shells (e.g. heat-denaturized albumin) or those self-assembled from molecular surfactants, mainly phospholipids. They show an increasing potential for drug delivery and bimodal imaging [7,8]. Microbubbles have recently attracted considerable attention for therapeutic application in enhancing blood-tissue permeability for drug delivery [9]. By introducing magnetic or semiconductor nanoparticles (NPs) on the bubble surface, multiple imaging modalities can be obtained. Microbubbles coupled with plasmonic silver or gold nanoparticles were shown to be very efficient dual ultrasound and optical contrast agents [10], or photoacoustic agents [11], and those coupled with superparamagnetic iron oxide nanoparticles are ideal candidates for ultrasound and magnetic imaging [12–15].

Different approaches to the nanoparticle incorporation into the microbubbles were proposed, depending on the shell composition and the nanoparticle type. In the case of thick and rigid polymeric shells, the microbubbles have very high stability and are not affected by the incorporation or adsorption of NPs. For microbubbles stabilized with long-chain phospholipids, coupling of nanoparticles (NPs) to the shell can be obtained by dispersing them in oil [16] or by using avidin-biotin conjugation [11]. When surfactants are used for microbubble stabilization, the nanoparticles may have strong effects on the microbubble stability because of the complex interactions between surfactant and NPs. These interactions have being intensively studied for foams stabilized in mixtures of NPs with oppositely charged surfactants [17]. In order to obtain the stabilization, the surfactant should form a hydrophobic monolayer on the NPs which corresponds to the near-zero value of the NPs zeta potential. However, if the surfactant concentration is too low or too high, the NPs are hydrophilic and do not adsorb at the air–water interface of the foam cell. Indeed, the stabilization of the foams using surfactant/NPs mixtures is due to the synergy between NPs and surfactant.

Highly fluorinated compounds have been widely used to fabricate stable microbubbles [18]. Most of phospholipid-based microbubbles investigated nowadays for medical applications are stabilized by a fluorocarbon gas [19,20]. Fluorocarbon gases were also found to exert an unexpected co-surfactant effect to the phospholipids forming the microbubbles' shell [21]. They were recently found to promote immobilization of fluorinated drugs and biomarkers into the microbubbles' phospholipid shell [22]. Using shell-forming amphiphiles containing perfluoroalkyl chains has a pronounced positive effect on the microbubble stability [23]. Microbubbles stabilized with long-chain semi-fluorinated phosphates were coupled with iron oxide nanoparticles without changing their stability [24].

Recently, we have synthesized water-soluble perfluoroalkyl phosphate surfactants $C_nF_{2n+1}(CH_2)_mOP(O)(OH)_2$ labeled *FnHm*Phos ($n = 8$ and 10, $m = 2$) which adsorption properties at the air-water interface can be mediated by the pH of the solution [25]. At neutral pH, these surfactants form super-elastic interfacial films with low surface tension and remarkably high surface elasticity. Subsequently, we have studied the stabilization of air microbubbles by *F8H2*Phos and have shown a direct correlation of the microbubble behavior with surfactant adsorption kinetics and interfacial properties [26].

In a previous paper, we have shown that *F8H2*Phos surfactant-stabilized air microbubbles were a good template for obtaining hollow microspheres with a shell composed of ferrite NPs [27]. The formation of these microspheres occurs at pH 7–8.5 in the presence of NaCl thanks to the synergy between the surfactant and the nanoparticles, and although both are negatively charged: the surfactant adsorbs rapidly on microbubbles and provides intermediate stabilization allowing the adsorption of NPs at the surface. Due to the fact that the NPs isoelectric point is very close to this pH, a low ionic force is sufficient to aggregate the NPs around the microbubbles, which contribute to stabilize them. The combination of NPs aggregation and the adsorption of soluble surfactant at the bubble surface favor the stabilization of hollow microspheres. In this paper, we show that hollow microspheres can be stabilized even when the conditions are less favorable, i.e. at higher pH when a stronger ionic force is required to screen the negative charges. We chose a surfactant with a longer fluorinated chain *F10H2*Phos that is low soluble at pH below 11. The microspheres prepared using *F10H2*Phos were found stable enough to withstand deposition on a solid substrate and drying. This was not the case with the microspheres obtained using *F8H2*Phos. We believe that this finding may provide a simple method to fabricate porous ceramics.

2. Experimental

2.1. Materials

All chemicals were of analytical grade, used without further purification. Iron chloride hexahydrate ($FeCl_3{\cdot}6H_2O$), 99% extra pure was purchased from Acros Organics, iron chloride tetrahydrate ($FeCl_2{\cdot}4H_2O$) reagent plus 99% from Sigma–Aldrich, hydrochloric acid (HCl) min 37% from Carlo Erba, tetramethylammonium hydroxide 25% w/w aqueous solution from Fluka (TMAH). Water was obtained from a MilliQ (Millipore) system (γ: 71.7 ± 0.2 mN m^{-1} at 20 °C; resistivity 18.2 MΩ cm).

2.2. Synthesis and characterization of Fe_3O_4 nanoparticles (NPs)

The synthesis of nanoparticles (NPs) was performed in two steps, using a controlled coprecipitation in a basic medium and a hydrothermal treatment, according to the protocol described previously [28]. In the first step, $FeCl_3{\cdot}6H_2O$, 1 M, and $FeCl_2{\cdot}4H_2O$, 2 M, were prepared by dissolving the salts in HCl, 2 M. 8 mL of the former and 2 mL of the latter were mixed and heated up to 70 °C for 15 min under mechanical stirring. Then, 26 ml of TMAH was added at a rate of 1.5 mL/min. A part of NPs was washed in water and dried for performing the structural and magnetic characterizations. The rest of the suspension was centrifuged and the precipitate washed in NaOH solution at pH 10 five times. Fresh suspensions of 5 mg/mL were used for bubble experiments.

The crystallographic structure of Fe_3O_4 NPs was checked by X-ray diffraction (XRD) using a Bruker D8 Advance diffractometer equipped with a quartz monochromator and Cu $K\alpha_1$ radiation ($\lambda = 0.154059$ nm). The lattice parameter, calculated from XRD patterns using UFIT and Powder Cell software, was found to be equal to $a = 0.8387(2)$ nm. To investigate the morphology, transmission electron microscope imaging (TEM) was performed with a TOPCON model 002B transmission electron microscope, operating at 200 kV, with a point to point resolution of 0.18 nm (see SI-1). The size of each particle was measured on TEM image by pointing the particle diameter and the distribution of the size has been determined using ImageJ software. The counting was performed on 150–200 particles.

2.3. Synthesis of F10H2Phos surfactant

The perfluoroalkylated phosphate $C_{10}F_{21}(CH_2)_2OP(O)(OH)_2$ (labeled *F10H2*Phos) was synthesized by phosphorylation with $POCl_3$ of the perfluoroalkylated alcohol precursor followed by hydrolysis as previously described [25]. Some properties of *F10H2*Phos are presented in Supplementary Information.