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Aqueous dispersion of metal oxide nanoparticles, using siloxane surfactants

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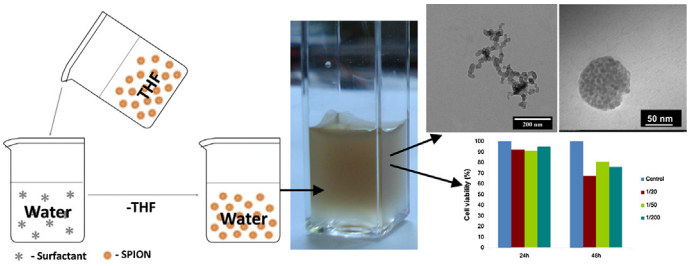
HIGHLIGHTS

- Siloxane surfactants were found biocompatible by MTT cytotoxicity tests.
- Stable water dispersions of SPION were obtained with these surfactants.
- Good cell viability was found for aqueous dispersion of metal oxide nanoparticles.
- Particles of 20–200 nm with different morphology were observed by TEM.
- SPION and an un-soluble drug can be dispersed together in surfactant vesicles.

GRAPHICAL ABSTRACT



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ABSTRACT

Siloxane surfactants containing tromethamol or carboxylate groups, with very good surface properties, are tested for the first time for biocompatibility using MTT cytotoxicity test. They are used for encapsulation of superparamagnetic iron oxide nanoparticles (SPION), and of a combination of these with nystatin as model un-soluble drug, in order to obtain stable aqueous dispersions. The initial magnetite and chromite nanoparticles have been synthesized previously by thermal decomposition thus being covered by dodecylamine and oleic acid. Their aqueous dispersions were obtained by physical methods using very low concentrations of siloxane surfactants, and were investigated by DLS, TEM, cryo-TEM and EDX. One such formulation was tested by MTT method and the results showed high cell viability. The nanoparticles covered with siloxane surfactants exhibited various types of morphology: individual particles, vesicle-like aggregates or composite particles, all having diameters roughly between 20 and 200 nm. The encapsulation of both SPION and nystatin confirmed our previous results on nystatin solubilization by encapsulation within the hydrophobic wall of surfactant vesicles.

1. Introduction

Over the past decades, various nanoparticles were explored for promising applications in the fields of material science, biology, and medicine. Superparamagnetic iron oxide nanoparticles (SPION) are characterized by dimensions under 15 nm [1]. As a consequence of their special properties, several new and exciting biomedical applications have been developed: contrast enhancing agents for MRI [2], drug delivery systems [3], magnetic hyperthermia [4], magnetically assisted transfection of cells [5–8].

Generally, the synthetic methods lead to nanoparticles with organic coatings, which are hydrophobic and allow them to be dispersed only in nonpolar or moderately polar organic solvents. In many cases, oleic acid is coordinated to the iron oxide nanoparticle

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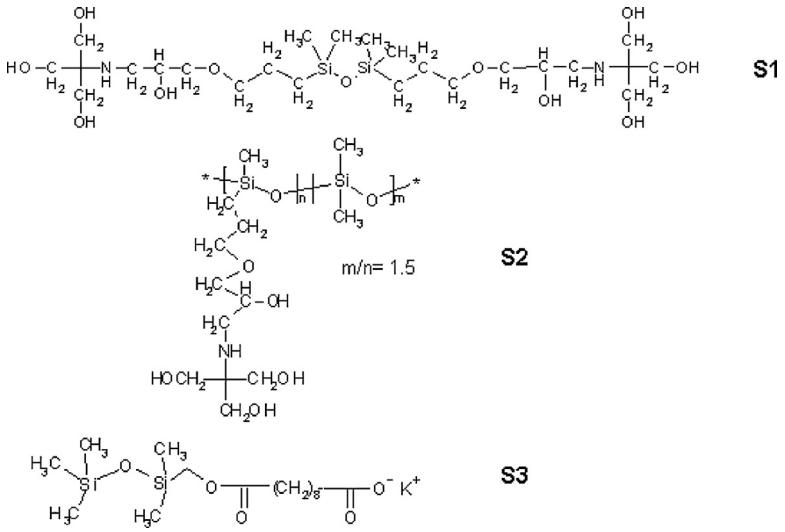

Scheme 1. Chemical structure of the siloxane surfactants.

surface through chemical bonding of the carboxylic acid group to the metal centers. For biomedical applications (and not only), replacement of the hydrophobic coating with a hydrophilic one is necessary, as to obtain stable aqueous dispersions. In order to ensure biocompatibility of SPIONs, several organic and inorganic coatings have been employed [4], including biocompatible polymers, polysaccharides, gold or silica. The surface modification of the hydrophobic capping of the nanoparticles may be done using modified poly(amidoamine) (PAMAM) dendrimers, polyethylene glycol (PEG) and folic acid [9–11], poly(acrylic acid, polyethylenimine, or glutathione [12]. The interaction of magnetic NPs with macrophages was tuned by coating the NPs with poly(DL-lactic acid-co-malic acid) (PLMA) and variable PEG content [2]. Certain strategies for water dispersal of magnetic NPs imply intercalation of amphiphilic molecules in the hydrophobic coating of the nanoparticles [9,13,14]. Cyclodextrine and Pluronic-type surfactants were reported to efficiently disperse oleic acid coated iron oxide NPs by phase transfer from hexane [15,16].

The type of encapsulation and the particle size affects the efficacy of iron oxide NPs as MRI contrast agents. It was found that the transverse relaxivity is greatly higher for a micellar system compared to polymer-coated particles using same-sized nanoparticles, while it increases with increasing particle size for the polymer-coated nanocrystals [17]. On the other hand, size-controllable nanoparticles composed of multiple metalic NPs synthesized by a supramolecular approach were found to exhibit collective effects, which enhance their efficacy [18]. The direct synthesis of water-soluble magnetite nanoparticles was also reported, using polyol solvent at elevated temperature [19] or vitamin C as ligand and stabilizer [20].

In the present work, we used oleic acid-coated magnetite (Fe_3O_4) or chrommite ($FeCr_2O_4$) nanoparticles that have been prepared by thermal decomposition method. These nanoparticles have been investigated by different specific methods and showed superparamagnetic behavior [21].

The siloxane-based surfactants are still insufficiently explored, although certain types of such surfactants are long known and even commercially available. However, they have low CMC values and unique performances in decreasing the surface tension of liquids and may exhibit both hydrophobic and oleophobic properties [22]. These characteristics make siloxane surfactants extremely attractive for nanoparticle stabilization in aqueous medium, when used in very small amounts. In addition, the siloxane-organic chemistry is very versatile, thus a very large diversity of hydrophilic molecules might be attached to the hydrophobic (poly)siloxane segment [23]. It is also accepted that polydimethylsiloxanes (PDMS) are characterized by physiological inertness and excellent compatibility with blood (low interaction with plasma proteins) [24].

We have reported a number of siloxane-containing surfactants [25–27] and tried to reveal their applicative potential especially for the stabilization of polymer or silver nanoparticles [25,26,28–31]. Besides this application, the micellar solubilization of poorly soluble drugs has also been demonstrated [32].

In order to consider a material for biomedical applications, it is imperative to ensure its biocompatibility. In many cases, although good results are obtained in terms of particle size and stability, the toxicity of the surface coating precludes the respective system from being effectively used in practice. It is known that polysiloxanes (silicones) of different architecture (cyclic, linear) and molecular weight are currently used in medical applications and cosmetic formulations. In our case, as we propose original surfactants, it is for the first time that any kind of biocompatibility test is reported.

As a continuation of our efforts in understanding the unique properties of siloxane-based surfactants, we describe here the biocompatibility of previously reported tromethamol-modified and carboxylate siloxanes, as well as the encapsulation of superparamagnetic nanoparticles using these particular surfactants, in order to vehiculate them in water. We also investigate the formation of complex drug-metal nanoparticles, using nystatin as model drug.

2. Experimental

2.1. Materials

The surfactants (S1–S3) (Scheme 1) were previously synthesized and characterized [26,27].

The precursors for iron oxide and iron-chromium oxide nanoparticles were prepared, using the following raw materials: iron(III) chloride ($FeCl_3{\bullet}6H_2O$), iron nitrate ($Fe(NO_3)_3{\bullet}9H_2O$), chromium nitrate ($Cr(NO_3)_3{\bullet}9H_2O$), calcium acetate ($(CH_3COO)_2Ca$), oleic acid ($CH_3(CH_2)_7CH{=}CH(CH_2)_7COOH$) and tetrahydrofuran (THF) from Sigma-Aldrich, trichloroacetic acid (CCl_3COOH) and dodecylamine ($CH_3(CH_2)_{11}NH_2$) from Fluka, glacial acetic acid, methanol and ethanol from Chemical Company. Nystatin (Nys) powder was obtained from Antibiotice SA (Iasi, Romania). Double distilled water was used for preparing the surfactant solution.