

POLYSILOXANE FLUID DISPERSIONS OF COBALT NANOPARTICLES IN SILICA SPHERES FOR USE IN OPHTHALMIC APPLICATIONS

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INTRODUCTION: Cobalt nanoparticles are of interest for biomedical applications because of their inherent higher magnetization relative to magnetite or maghemite. The bulk saturation magnetization of cobalt is theoretically 1400 emu/cm³ while magnetite or maghemite is about 400 emu/cm³ [1]. We have previously reported that nanophase-separated PDMS-PCPMS-PDMS triblock copolymers (Figure 1) can be effective

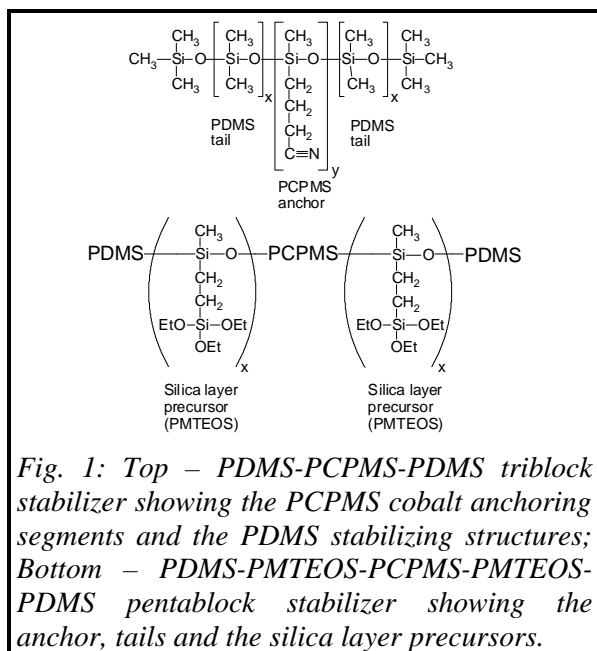


Fig. 1: Top – PDMS-PCPMS-PDMS triblock stabilizer showing the PCPMS cobalt anchoring segments and the PDMS stabilizing structures; Bottom – PDMS-PMTEOS-PCPMS-PMTEOS-PDMS pentablock stabilizer showing the anchor, tails and the silica layer precursors.

steric dispersion stabilizers for colloidal cobalt particles in polydimethylsiloxane (PDMS) carrier fluids [2-3]. The central nitrile-functional blocks coordinate with the cobalt surface as a so-called "anchor" block and the polydimethylsiloxane "tail" blocks extend into the PDMS to stabilize the particles in the dispersion. These fluids have saturation magnetizations of approximately 100 emu/g of cobalt, but magnetic measurements made over time show that their magnetic susceptibility decreases with aging for dispersions in contact with an air-containing atmosphere. This has been attributed to surface oxidation [3].

This paper describes our work on inhibiting environmental oxidation of magnetic cobalt nanoparticles by coating them with silica shells (Figure 2). Dicobalt octacarbonyl has been thermolyzed in the presence of PDMS-PMTEOS-

PCPMS-PMTEOS-PDMS pentablock copolymers (figure 1). The PCPMS central block binds the cobalt and the PDMS tail blocks sterically stabilize the cobalt dispersion as described previously [2-3].

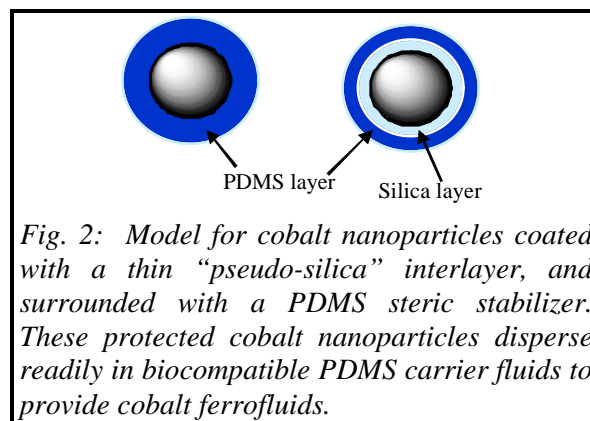


Fig. 2: Model for cobalt nanoparticles coated with a thin "pseudo-silica" interlayer, and surrounded with a PDMS steric stabilizer. These protected cobalt nanoparticles disperse readily in biocompatible PDMS carrier fluids to provide cobalt ferrofluids.

The PMTEOS blocks serve as precursors for the nanoparticle coating process. Since these precursor blocks are covalently bound to the segment which is coordinated to the cobalt nanoparticle surfaces, these silica precursors are uniquely positioned to form a tight "pseudo-silica" protective interlayer. After forming the nano-cobalt, the PMTEOS blocks are condensed to form a thin protective layer at the nanoparticle surfaces. Oxidative aging studies are underway, and will be reported in a separate paper in this symposium [4]. It appears that coating the particles with silica can retard any oxidation kinetics significantly.

METHODS: *Synthesis of PDMS-PMVS-PCPMS-PMVS-PDMS pentablock copolymers (PMVS is poly(methylvinylsiloxane)).* A procedure for preparing a copolymer with 15000 g/mol PDMS, 2000 g/mol PMVS and 2000 g/mol PCPMS blocks is provided. The first part of the copolymer synthesis involves preparing controlled molecular weight PCPMS oligomers with terminal lithium siloxanates. D₄CN (12.5 g) and 0.24 g (0.01 mol) lithium hydroxide were charged to a 500-mL roundbottom flask equipped with a mechanical stirrer and nitrogen purge. The mixture was stirred at 140 °C for at least 48 hours to reach thermodynamic equilibrium. The ratio of cyclics to linear species at equilibrium monitored by GPC was 27 wt% small cyclics and 73 wt% linear chains. After equilibrium was achieved, 250 mL

of dichloromethane was added to the macroinitiator via cannula. Twenty-two mL of trimethyltrivinylcyclotrisiloxane (D₃-vinyl) was added along with 12.5 mL THF as a reaction rate promoter (\approx 5 vol.% of the total volume). Five volume percent of the promoter was added to all block copolymer reactions irrespective of the block molecular weights. ¹H NMR was used to monitor the reaction progress by observing the disappearance of the signals at 0.23 ppm from the methyl protons in D₃-vinyl and the appearance of the signals at 0.14 ppm owing to methyl protons in linear PMVS blocks. After the reaction reached 85% conversion, the solution was transferred to a flame dried 1000-mL roundbottom flask filled with argon via cannula. A 200-mL aliquot of a D₃-dichloromethane solution (0.85 g D₃ per mL) was added along with an additional 20 mL THF. Another 150 mL of dichloromethane was added to bring the reaction volume to \approx 600 mL and to obtain a clear solution. The disappearance of the D₃ protons at 0.14 ppm was monitored by ¹H NMR. The reaction was allowed to proceed at room temperature to obtain 85% monomer conversion. The pentablock copolymer was terminated with an excess of trimethylchlorosilane (4.4 mL) via syringe and stirred for 30 minutes. The solution clouds upon termination due to precipitation of LiCl. The excess trimethylchlorosilane and the dichloromethane solvent were removed under reduced pressure. The viscous copolymer was diluted with chloroform and washed repeatedly with water to remove the lithium chloride. The copolymer-chloroform solution was precipitated into methanol to remove nitrile containing siloxane cyclics (from the central block equilibration step) and the THF promoter. The methanol phase was decanted, and the polymer was dried at 80 °C under vacuum overnight. The block molecular weights and the total molecular weights of the triblock copolymers after purification were established using a combination of titration and NMR measurements.

Synthesis of PDMS-PMTEOS-PCPMS-PMTEOS-PDMS protective steric stabilizers. An exemplary procedure describes a hydrosilation reaction of a pentablock copolymer containing 2000 g/mol PMVS, 2000 g/mol PCPMS, and 15000 g/mol PDMS blocks with triethoxysilane in a 2000 g/mol PDMS carrier fluid. Variations of this reaction were conducted in either toluene, octamethylcyclotetrasiloxane (D₄), hexamethyldisiloxane or cyclohexane as reaction media. An important advantage of using low molecular weight solvents over using 2000 g/mol PDMS is that the sol-gel reactions can be

conducted under relatively dilute conditions, then they can be removed in vacuo to concentrate the magnetic component in the mixture.

The reaction apparatus consisting of a 250-mL 2-neck roundbottom flask equipped with a mechanical stirrer and argon purge was flame-dried under argon. Twenty mL of 2000 g/mol PDMS and 1g of a PDMS-PMVS-PCPMS-PMVS-PDMS pentablock copolymer were charged with stirring. Triethoxysilane (0.25 mL) and 0.09 mL (0.5 wt%) platinum divinyltetramethyldisiloxane complex catalyst (Karstedt's catalyst) in xylene (2.1–2.4 wt % Pt) were charged to the reaction flask with stirring to hydrosilate the vinyl-containing blocks with Si-H groups from triethoxysilane. A stoichiometric ratio of triethoxysilane to vinylsilane units was used in all cases. The reaction was allowed to proceed for 2-3 days at 55 °C. ¹H NMR was used to monitor the reaction progress by observing the disappearance of vinyl peaks (δ =5.8-6.1 ppm) and the Si-H peak (δ =4.3 ppm). Approximately 2000 g/mol PDMS carrier fluids were prepared by the equilibrium ring-opening polymerization of D₄ with triflic acid as a catalyst. The detailed discussion of the carrier fluid synthesis has been reported previously [2].

Synthesis of a cobalt nanoparticle dispersion and formation of the silica protective layer. One gram of Co₂(CO)₈, 1 g of a PDMS-PMTEOS-PCPMS-PMTEOS-PDMS pentablock copolymer and 20 mL of solvent were dissolved at room temperature irrespective of the reaction medium. The reaction proceeded at 45 °C for 45 min. The reaction temperature was raised to 120 °C to yield a greenish-brown solution and maintained at this temperature for 16 h for reactions conducted in 2000 g/mol PDMS or 2 h for the reactions conducted in other solvents. Upon reaction completion, the mixture was slowly cooled to room temperature under an argon purge. The reaction mixture was diluted with 80 additional mL of solvent when using hexamethyldisiloxane, D₄ or toluene, but was not diluted for the case of using PDMS as the solvent. Thirty-five μ L of O₂-free water was added along with 21 μ L of dibutyltin diacetate (DBTA) catalyst to condense ethoxysilanes and form a "pseudo-silica" network. The dispersion was stirred at room temperature under argon for a week. The concentration of water added to the reaction was estimated from the concentration of ethoxy groups in the copolymers. One mole of water was used for every two moles of ethoxy groups.

Specified cobalt concentrations of the reactions conducted in 2000 g/mol PDMS carrier fluids were

achieved by introducing an appropriate amount of PDMS at the beginning of the reaction to obtain the targeted cobalt concentration. For reactions conducted in other solvents, dispersions with specified cobalt concentrations in PDMS carrier fluids were prepared by transferring an aliquot of the silica-coated cobalt dispersion in the original solvent to a vial, diluting the sample with the desired amount of PDMS, and then removing the solvent under reduced pressure.

Characterization: TEM micrographs were obtained using a Philips 420T TEM run at 100kV. The TEM samples of the cobalt dispersions were prepared by diluting the dispersions with toluene to obtain the color of “weak tea.” The solutions were cast onto a carbon-coated grid and the toluene was evaporated. Magnetization measurements of the cobalt fluids with specified cobalt concentrations were made on a Standard 7300 Series Vibrating Sample Magnetometer (VSM) System (Lake Shore Cryotronics, Inc.). Measurements were made in applied fields ranging from 8000 Oe to -8000 Oe with 0.1 emu sensitivity.

RESULTS AND DISCUSSION: The materials have been developed to function in specific clinical applications. The first application is for a silicone magnetic fluid for use in retinal detachment surgery. This application requires long-term placement of the nanocobalt dispersion in the eye. The silica coating is necessary to provide protection against local and systemic toxicity, and to provide stable magnetic properties over time. The second application for coated cobalt nanoparticles is magnetic field-directed drug delivery. The polymer dispersants in this case will require modification to make them hydrophilic. This application requires the same protection against toxicity, and also requires strict size regimentation into the 10nm range to facilitate renal excretion of the nanoparticles.

The formation of silica-protected cobalt nanoparticle dispersions in PDMS fluids can be considered in three steps: (1) Formation of the magnetic cobalt nanoparticles, (2) Condensation of the “pseudo-silica” protective interlayer at the cobalt surface, and (3) Transfer of the protected cobalt particles to PDMS with concurrent concentration of the cobalt as the reaction solvent is removed. One principle in the cobalt formation step was to design reaction conditions whereby the organocobalt precursor would diffuse into the core of block copolymer micelles (formed by the stabilizer in solution) and would react within that core. This yields well-coated, non-aggregated cobalt nanoparticles [2-3]. Ethoxysilane groups in the copolymers were then condensed essentially to

form silica shells around the particles and inhibit oxidation. It is important to conduct this step in a reaction medium that allows the PMTEOS precursor block of the stabilizer to contract, tightly condense, and form a “pseudo-silica” thin film on the particle surfaces. We hypothesize that the nature of the interaction between the blocks comprising the silica layer precursor (PMTEOS) with the solvent for this step is an important consideration to achieve “tight” protective layers. If these blocks extend too far into the solvent, inter-particle condensation rather than the desired intra-particle condensation may be significant.

Toluene is a good solvent for PDMS but a poor solvent for PCPMS. We have previously conducted both surface tension measurements and dynamic light scattering of toluene solutions of PDMS-PCPMS-PDMS triblock copolymers and the results suggest the desired micellar structures which are probably the reaction sites for particle formation [2]. It is hypothesized that the pentablock copolymers also form micellar solutions in D₄, hexamethyldisiloxane, and 2000 g/mol PDMS, where the PCPMS is concentrated in the micelle cores and long PDMS tail blocks protrude outward into the media to form the micelle coronas. PMTEOS blocks located between PDMS and PCPMS blocks are able to form a silica layer around the particles during the sol-gel process.

Dicobalt octacarbonyl was dissolved in pentablock micellar solutions at room temperature, then the mixtures were heated to evolve the carbon monoxide ligands. In all cases, this step of the reactions was conducted using 1g of copolymer and 1g of Co₂(CO)₈ in 20 mL of the reaction medium. Further discussion of similar cobalt dispersion reactions using triblock stabilizers have been reported previously [2-3]. Thermolysis of the dicobalt octacarbonyl to form magnetic cobalt nanoparticles encased in pentablock copolymers was successful in hexamethyldisiloxane, PDMS, D₄ and toluene, but not in cyclohexane. These cobalt dispersions were transparent, dark red-brown liquids.

The cobalt nanoparticles prepared in toluene, hexamethyldisiloxane and PDMS have an average particle diameter of 10 nm with relatively narrow size distribution. As will be further described below, D₄ appears to be a particularly promising solvent for these reactions, but early results show a somewhat bimodal particle size distribution, and further investigation will be required (figure 3).

One objective has been to investigate effects of the nature of the solvent in the sol-gel condensation step (step 2) with respect to how tightly the silica layer forms around the particle surfaces. Small (stoichiometric) amounts of O₂-free water and

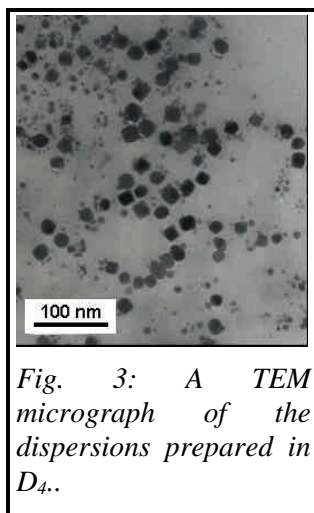


Fig. 3: A TEM micrograph of the dispersions prepared in D₄.

DBTA catalyst were introduced into the stable cobalt dispersions (in toluene, D₄, hexmethylsiloxane and 2000 g/mol PDMS) to condense ethoxysilane pendent groups. Quantitative reaction conditions were established by monitoring the elimination of ethanol using ¹H NMR. Some aggregation was observed when the sol-gel reactions were conducted in hexamethyldisiloxane, but the other solvents produced stable silica-protected cobalt nanoparticle dispersions.

The final step in the process is to concentrate the dispersions as they are transferred to PDMS to increase the magnetic response of the desired PDMS fluids. While PDMS is an effective solvent for forming the particles, it cannot be easily removed due to its polymeric nature. Early results from this phase of the research show that aggregation occurs during the concentration step if the particles are produced in toluene, but that no aggregation occurs when the protected particles are synthesized in D₄ (Figure 3). Early studies suggest that a bimodal particle size distribution can form, and control over this aspect will require further investigations. A significant decrease in magnetic susceptibility of the dispersions prepared in toluene was also observed upon concentration, whereas the magnetic susceptibility of those prepared in D₄ is promising. Consequently, the use of D₄ as a reaction solvent may allow for a significant increase in the magnetic susceptibility of a material since higher cobalt concentrations can be achieved.

Magnetic properties of the cobalt dispersions conducted in PDMS were monitored during the sol-gel reactions. Approximately 10% loss in saturation magnetization occurs during the process (Figure 4). The dispersions containing silica-coated particles prepared in 2000 g/mol PDMS were sealed under argon or air-containing atmospheres to study their oxidative stability over time. These early magnetic measurements indicate

that coating the particles with silica thin films inhibits oxidation. Results suggest some loss in magnetic properties in the first two months, then the materials appear to stabilize. These aspects will undoubtedly require longer-term aging studies. The aging characteristics of stable dispersions containing higher concentrations of cobalt prepared in D₄ are also under investigation.

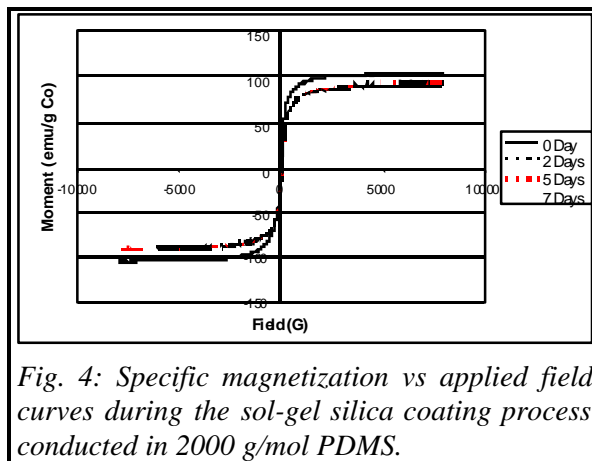


Fig. 4: Specific magnetization vs applied field curves during the sol-gel silica coating process conducted in 2000 g/mol PDMS.

CONCLUSIONS: Well-defined cobalt nanoparticle dispersions have been successfully prepared in D₄ and 2000 g/mol PDMS carrier fluids in the presence of PDMS-PMTEOS-PCPMS-PMTEOS-PDMS pentablock copolymer micelles. This copolymer fills the dual role of both a dispersion stabilizer and a precursor for a protective nanoparticle coating process. Nanoscale particles (on the order of 10-20 nm in diameter) result. Magnetic measurements suggest that coating the nanoparticles with silica thin films slows the oxidation process significantly.

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