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Emulsions stabilized with organic solid particles

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ABSTRACT

Biodegradable and biocompatible o/w emulsions were prepared using triglyceride oil and solid organic particles made of block copolymer nanoparticles as stabilizers (Pickering emulsions). In order to reach high concentration of internal phase, rather concentrated dispersions of nanoparticles were required. Nanoparticles of poly(caprolactone)-*block*-poly(ethylene oxide) (PCL-*b*-PEO) diblock copolymer were obtained using the "nanoprecipitation" process relying of the spontaneous emulsification upon solvent shifting. The classical "nanoprecipitation" process was improved so as to afford more concentrated suspensions of nanoparticles, and the nanoparticles were characterized by means of dynamic light scattering and ^{1}H NMR spectroscopy. The process allowed the preparation of aqueous dispersions of PCL-*b*-PEO nanoparticles with 35–50 nm diameter at concentrations over 5 wt.%. In D_2O, the PCL blocks formed a central hydrophobic core of reduced mobility, while the PEO blocks formed a hydrophilic corona layer swollen by water. O/w emulsions of medium chain triglycerides were successfully prepared using the suspensions of PCL-*b*-PEO nanoparticles as stabilizers. Typical droplet sizes were between 2 μm and 15 μm. The emulsions showed great stability upon storage and their particle size distributions did not show excess nanoparticles present in the aqueous phase as submicron nanoparticles, even when large amounts of nanoparticles with respect to oil were used. The mean droplet diameter of emulsions was controlled by the mass ratio *M*(oil)/*M*(nanoparticles). SANS and TEM experiments performed on PCL-*b*-PEO nanoparticles and micelle-stabilized emulsions disclosed a rearrangement of the nanoparticles at the oil/water interface due to the liquid state of the micelle core of PCL.

1. Introduction

Pickering emulsions are stabilized by solid particles in place of surfactants [1]. Their "surfactant-free" character makes them attractive for cosmetic and pharmaceutical application where surfactants often show adverse effects (irritancy, hemolytic behavior, etc.) [2]. Towards such domains, biocompatible and biodegradable Pickering emulsions would be an obvious benefit. They can be made up from the oils used in pharmaceutical applications, and organic solid particles made from biodegradable materials. Since solid stabilizing particles are necessarily smaller than emulsion droplets, solid particles of nanometric size were selected so as to allow the fabrication of Pickering emulsions over a wide droplet size range. There are two issues to be overcome in order to reach such goal: (i) the choice of organic nanoparticles that are partially wet by water and oil in order to ensure their anchoring to the oil/water interface; and (ii) the preparation of suspensions of solid particles of high enough concentration in order to allow full coverage of the droplet surface, even for concentrated emulsions of small droplets that have a large interfacial area. The purpose of the present research is the preparation of such emulsions stabilized by block copolymer nanoparticles. This can be achieved if the two issues quoted above receive satisfactory answer.

Solid particles can spontaneously adsorb at fluid interfaces forming either a dense monolayer of particles, or a thick layer of aggregated solid particles that behaves as a rigid stabilizing layer acting against coalescence [3,4]. Many types of solid particles (hydrophilic silica, hydrophobic silica, clay, barium sulfate, calcium carbonate, polystyrene, spores, etc.) [1,5–12] were used to stabilize emulsions.

Biodegradable nanoparticles would decrease the risk of toxicity already observed with a lot of common chemical surfactants and inorganic nanoparticles, and they are expected to create a barrier to diffusion that allows a controlled release of drug substances incorporated either in the oily layer or inside the polymeric nanoparticles. Poly(caprolactone)-*block*-poly(ethylene oxide) (PCL-*b*-PEO) copolymers have raised much interest because they are biocompatible and partly biodegradable [13–16]. The PCL block is made of biodegradable polyester, and the PEO block is a water-soluble polymer of low molar mass that is bioresorbable.

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Such block copolymers are ideal candidates for application of emulsions to pharmaceutical or cosmetic domains.

This work firstly deals with the preparation of particles of non-ionic amphiphilic diblock copolymers that contain a hydrophilic poly(ethylene oxide) (PEO) block and a hydrophobic poly(ε-caprolactone) (PCL) using a modified nanoprecipitation process. In a second time, those nanoparticles are used to stabilize o/w emulsions made with medium chain triglyceride (MCT) as oil. Such particles are often called "block copolymer micelles" although they are better particles than classical micelles. Indeed classical micelles formed with water-soluble surfactants form spontaneously, and are at equilibrium with a residual soluble fraction in water. Block copolymer micelles do not form spontaneously and the residual concentration of block copolymer in solution is vanishing low. In the literature, the preparation processes of block copolymer micelles consist in either dialysis of organic solution of block copolymer or the present nanoprecipitation method. The term "Block copolymer nanoparticles" will be used throughout the whole paper. Block copolymer nanoparticles were characterized for their size and internal structure using dynamic light scattering, transmission electron microscopy, and ^{1}H NMR measurements. Oil-in-water emulsions were prepared using a conventional mechanical shearing process. Lastly, small-angle neutron scattering (SANS) experiments were used for investigating the structure of the interfacial layer at the oil/water interface where the presence of micelles was expected.

2. Experimental

2.1. Materials

Epsilon-caprolactone (ε-CL) (Sigma–Aldrich) was purified by vacuum distillation over calcium hydride (CaH_2, Acros Organics). Poly(ethylene glycol) monomethyl ether (mPEG) with of molar mass 5000 g mol^{-1} (Sigma–Aldrich) was dried by azeotropic distillation of toluene (anhydrous toluene, Sigma–Aldrich). Acetone (Laurylab), dichloromethane (Acros Organics), stannous 2-ethylhexanoate ($Sn(Oct)_2$, Sigma–Aldrich), deuterated water (D_2O) and dodecane-*d26* (Eurisotop, Saclay, France) were used as received. Deionized water of 18 MΩ cm^{-1} resistivity was used throughout the work.

2.2. Methods

2.2.1. Synthesis of the PCL-b-PEO diblock copolymer

mPEG was dried by azeotropic distillation of its solution in anhydrous toluene under dry nitrogen atmosphere. The PCL-*b*-PEO diblock copolymer was synthesized by ring-opening polymerization of ε-CL with mPEG as a macroinitiator and stannous 2-ethylhexanoate as a catalyst [14,16–19]. A determined amount of ε-CL, mPEG, and $Sn(Oct)_2$ (0.1 mol% of ε-CL) were weighted into a rounded three-necked glass flask equipped with a magnetic stirring bar. The reactor was closed under dry nitrogen and heated in an oil bath at 130 °C for 12 h. The reaction mixture was cooled down to room temperature, and the block copolymer was precipitated in an excess of cold diethyl ether. The copolymer recovered by filtration was purified by precipitation of its solution in dichloromethane into an excess of cold diethyl ether. Finally the mixture was filtered and dried at room temperature under vacuum for 24 h. The mean degree of polymerization of the PCL block was determined by ^{1}H NMR spectra (Fig. 1) and size exclusion chromatography (SEC) as shown in Table 1. At the end, the block copolymer chemical formula is PCL_{65}-*b*-PEO_{113}. This block copolymer was not soluble in water [14].

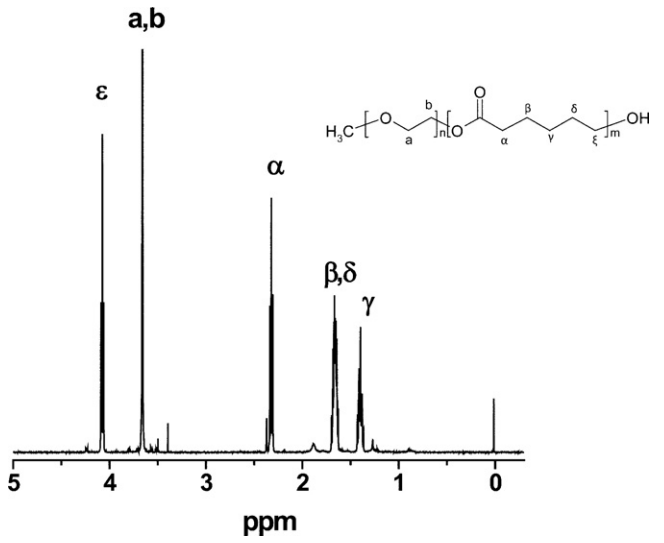

Fig. 1. ^{1}H NMR spectrum of PCL-*b*-PEO in $CDCl_3$ and the assignment of the lines.

2.2.2. Preparation of aqueous dispersions of block copolymer nanoparticles

Nanoparticles were prepared using the spontaneous emulsification process [20]. This method was modified in order to increase the concentration of solid particles beyond the usual limits of the nanoprecipitation process. As a typical recipe, 0.75 mg of PCL-*b*-PEO was first dissolved in 50 mL of acetone and then introduced drop wise in 15 mL of water under gentle stirring. The acetone was evaporated under reduced pressure in a second stage.

2.2.3. Preparation of emulsions

The MCT oil and aqueous suspension of PCL-*b*-PEO micelles were mixed together with an UltraTurrax® T25 device equipped with a S25N-18G shaft (IKA, Germany) rotating at 22,000 rpm during 5 min (cold process) and an o/w emulsion was obtained.

2.2.4. NMR analyses

^{1}H NMR spectra of PCL-*b*-PEO diblock copolymer were recorded by using a Brucker DRX 300 spectrometer operating at 300 MHz. Either deuterated chloroform ($CDCl_3$) or deuterated water (D_2O) were used as solvents. Chemical shifts were measured in ppm from tetramethylsilane.

2.2.5. Size exclusion chromatography

Size exclusion chromatography (SEC) measurements were performed with a Viscotek TDAmax system from Malvern Instruments that consists of an integrated solvent and sample delivery module (GPCmax) and a Tetra Detector Array including a right (90°) and low (7°) angle light scattering detector (RALS/LALS), a 4-capillary differential viscometer, a differential refractive index detector, and a Diode Array UV Detector. THF was used as the mobile phase at a flow rate of 1 mL min^{-1}; toluene has served as a flow rate marker. All polymers were injected after filtration through a 0.45 μm pore-size membrane. The separation was carried out on three Polymer Laboratories columns [3× PLgel 5 μm Mixed C (300 × 7.5 mm)] and a guard column (PL gel 5 μm). Columns and detectors were maintained at 40 °C. The OmniSEC 4.6 software was used for data acquisition and data analysis. The absolute molar mass was calculated using triple detection from combined LS and RI signals. The average refractive index increment (d*n*/d*C*) was measured with the online refractometer injecting polymer solutions at different concentrations. Then, the d*n*/d*C* can be calculated by plotting the RI area (integrated from the RI signal) versus injected concentration