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Synthesis and characterization of environmentally benign, semifluorinated polymers and their applications in drug delivery

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ABSTRACT

We describe the synthesis, physicochemical studies and pharmaceutical assessment of a class of pegylated semifluorinated amphiphilic block-copolymers based on short pendant fluorinated side chains attached to moderately hydrophobic units. These polymers allowed us to investigate how the balance between hydrophobicity and fluorophilicity in the polymer can be tuned to match that of small molecules to be used in drug delivery. Remarkably, we found that using short perfluoroethyl groups in the polymer allows the preferential stabilization of nanoemulsions based on isoflurane, a fluorinated anesthetic made partly hydrophobic by the presence of a chlorine atom. In comparison, nanoemulsions of sevoflurane, a purely fluorophilic anesthetic, were not as stable. The lipophilicity of the polymers was also investigated in regards to solvation of hydrophobic molecules. Surface properties such as critical micelle concentration (CMC) and surface tension demonstrated the uniqueness of these fluorinated amphiphiles. Finally, the use of short perfluoroethyl chains makes these polymers environmentally benign in terms of bioaccumulation and toxicity.

1. Introduction

Perfluorinated compounds are heavily utilized [1] in fire-fighting applications, cosmetics, paints, lubricants and pharmaceutical formulations [2]. However, longer chain fluorocarbons have been replaced for general use in the US with short-chain perfluoroethers. This was done out of concern for bioaccumulation and general toxicity [3]. Specifically, perfluorooctanoic acid (PFOA) and perfluorooctanesulfonic acid (PFOS), which were used as surfactants during the synthesis of perfluorinated polymers, have received the most attention after their detection in places ranging from remote areas in the Arctic to blood samples of the general U.S. population [4,5]. Perfluorocarbon bioaccumulation and toxicity tend to increase with longer chain length, with groups composed of four perfluorinated carbons (perfluorobutyl) or less being considered safe for humans [2–4].

Short fluorocarbons are used in a variety of industrial materials. For instance, the OMNOVA Polyfox© line lists polymers in which short perfluoroethers are used for the purpose of achieving optimal properties in paints and coatings. The Polyfox© surfactants are synthesized commercially by polymerization of fluorinated oxetane monomers, using a Lewis acid catalyst and nucleophilic initiator [5,6]. The most common fluorocarbon used is a perfluoroethyl, a fluorous group significantly shorter than longer fluorocarbons that have shown toxicity and bioaccumulation [6]. These issues have been shown to decrease with shortening of fluorous molecules to six carbons or less [4,7]. The Polyfox© line has undergone all required environmental and health related studies and has been granted full regulatory approval by The United States EPA, allowing for the manufacture and sale of these environmentally-benign products [8].

Pharmaceutical applications of perfluorocarbon derivatives are based on the unique physicochemical properties of fluorous compounds, including thermal and chemical stability, biological inertness, high surface tension, and the ability of dissolving large amounts of oxygen. Previous studies have shown that highly fluorinated amphiphilic diblock copolymers can successfully be used for emulsifying fluorous anesthetics in drug delivery applications [9–11]. With the inclusion of perfluorooctyl bromide (PFOB), an FDA-approved additive, these polymers were shown to stably emulsify sevoflurane (Fig. 1) at concentrations up to 20–30% v/v, a significant increase over the 3.5% v/v concentration of sevoflurane that can be achieved with a classical hydrophobic emulsion as Intralipid [11]. In contrast, the same polymers were

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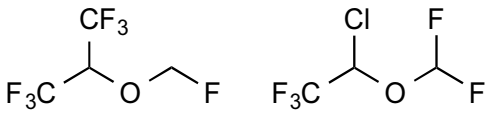


Fig. 1. Chemical structures of sevoflurane and isoflurane.

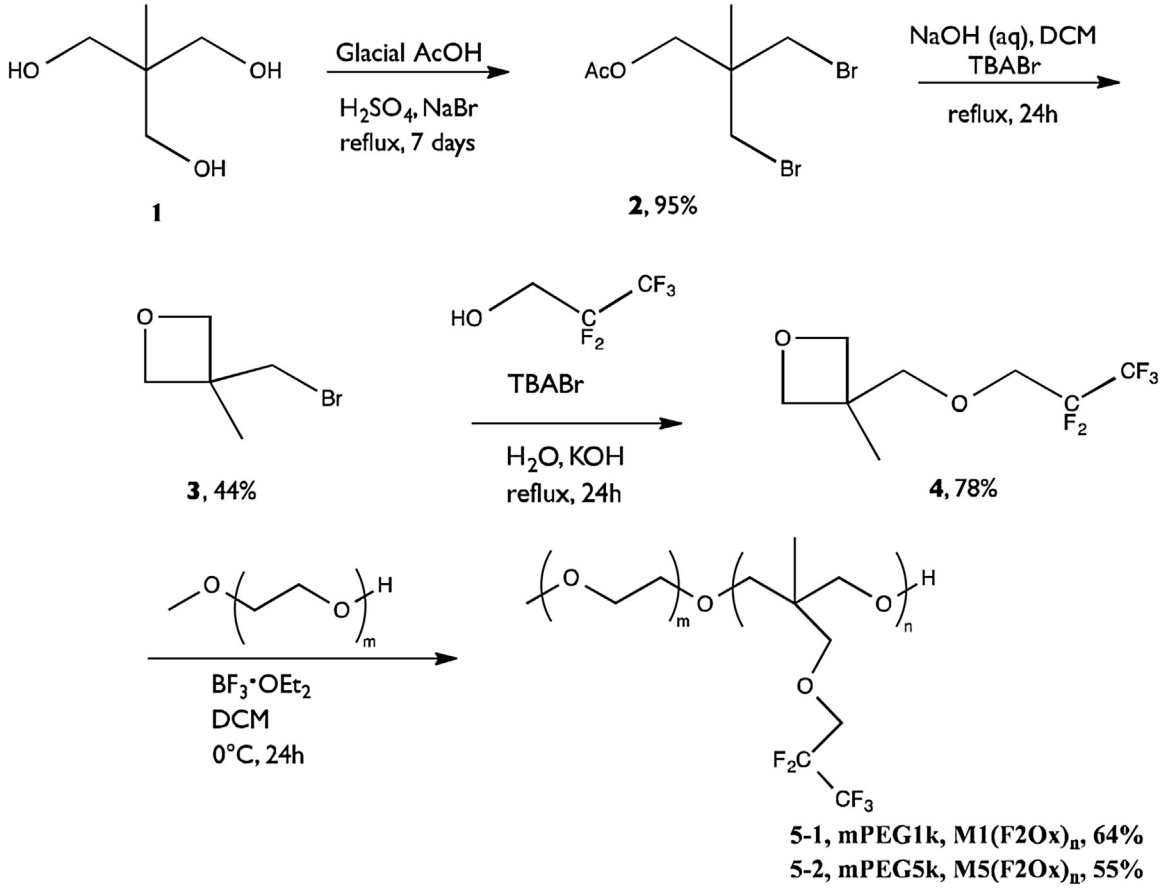
not able to stabilize properly emulsions of isoflurane (Fig. 1), likely due to the increased lipophilicity of this compound as opposed to sevoflurane. Due to a chloride substitution for one trifluoromethyl group, isoflurane has a lower fluorine content than sevoflurane (51% w/w *vs*. 67% w/w), making the molecule more lipophilic. To date, the best formulations to emulsify isoflurane are based on classical surfactants and provide a concentration of anesthetic between 8 [12] and 15% v/v [13]. We reasoned that in order to stably emulsify this anesthetic, a surfactant must include a balance between fluorophilicity and lipophilicity that would be close or match that of isoflurane. The new diblock copolymer described below is composed of a very short hydrophobic backbone to which a pendant perfluoroethyl is attached, similarly to the composition of some of the OMNOVA Polyfox© polymers. Pegylation of this small oligomer leads to the formation of an amphiphilic polymer, which is highly water-soluble and can be used to efficiently emulsify isoflurane when using a specific size of the hydrophobic/fluorophilic perfluoroether moiety.

2. Results and discussion

2.1. Polymer synthesis

The synthesis of these block co-polymers was adapted from patents [14,15] and earlier work done in our group [16] (Scheme 1). In glacial acetic acid, the triol, 1,1,1-tris(hydroxymethyl)ethane (**1**), was treated with sulfuric acid and sodium bromide to generate hydrogen bromide *in situ* to give the dibrominated product, 3-bromo-2-bromomethyl-2-methylpropyl acetate (**2**), as the major substitution product. Under biphasic conditions, the acetate was cleaved with sodium hydroxide allowing for *in situ* cyclization to give 3-(bromomethyl)-3-methyloxetane (**3**). This was then functionalized with 1H,1H-pentafluoropropan-1-ol. This reaction was found to work best under phase transfer conditions. Both oxetane monomers (**3** and **4**) were purified by distillation, but yields were lower than expected due to the high volatility of these molecules. Pegylation was achieved by using the terminal alcohol of methoxy polyethylene glycol (mPEG) as a macroinitiator in the presence of boron trifluoride diethyl etherate to carry out a ring-opening polymerization of the fluorous oxetane. Two methoxy polyethylene glycol lengths of 1000 and 5000 g/mol were used to make different diblock copolymers and explore their ability at emulsifying and encapsulating lipophilic and fluorophilic molecules.

Resulting polymers were purified by an automated CombiFlash® system. Polymerization yielded products with 3–10 oxetane monomers added. Four different fractions, composed of a mixture of perfluoroether telomers added were isolated. The



Scheme 1. Synthesis of $M_x(F2Ox)_y$. Note on nomenclature: M corresponds to mPEG, with the following number being the average molecular weight. (F2Ox) indicates the opened oxetane monomer with a perfluoroethyl side chain.

mPEG-1000 polymers contain a 3–4 and 4–5 unit fractions, while the mPEG-5000 contains fractions composing of 3–5 and 7–9 units added. This polydispersity agrees with similar behavior reported in the literature [17,18].

2.2. Physicochemical characterization

Dynamic light scattering (DLS) was applied to measure the average size of the amphiphilic aggregates in solution. The particle size data are summarized in Table 1. As expected, as the length of hydrophobic chain increases, so does the aggregate size. The polymer sizes are consistent with known micelle-forming fluorocarbon polymers according to PEG size [9]. Note that cryogenic transmission electron microscopy (cryo-TEM) is commonly used to validate the aggregate shape. However, these amphiphiles contain a relatively small hydrophobic core compared to a large mPEG chain, which is highly solvated and indistinguishable from vitrified water [19].

The critical micelle concentrations (CMC) of these polymers were estimated by measuring the surface tension of polymer solutions at various concentrations. Increasing the concentration of the polymer under the CMC leads to a linear decrease in the surface tension. At the CMC, micelle formation begins and any additional surfactant will aggregate and not affect the surface tension any longer. It has been shown that substitution of fluorine atoms for hydrogen decreases an amphiphile's surface activity for aqueous solutions, which promotes micellization at lower concentrations [20]. The CMC was unaffected by the length of hydrophilic segment (PEG), but had a slight increase as more hydrophobic monomers were added.

To evaluate the lipophilicity of the aggregate's core, attempts at solubilizing a lipophilic molecule were undertaken. We used the anticancer agent paclitaxel as a model lipophilic small molecule. We found that the presence of short fluorocarbons in the micelle core prevents the binding and encapsulation of purely hydrophobic molecules. This result suggests that the micellar core is not adequately lipophilic for drug encapsulation, which makes sense, as there are pendant fluorous chains throughout which repel molecules that are not fluorophilic.

2.3. Emulsion stability

The results on the poor loading of lipophilic molecules within the micellar core suggest that the polyoxetane block is more fluorophilic than lipophilic. To test this conclusion, the emulsification of fluorinated anesthetics was studied, specifically looking at possible differences between the fluorophilic sevoflurane and the more lipophilic isoflurane (Fig. 2). Previous studies have shown that PEG-based copolymers with a fluorocarbon core can form stable emulsions with sevoflurane. The polymers used in those studies typically contained a purely fluorophilic fluorocarbon chain with more than eight carbon atoms [9,10]. In contrast, use of polymers with perfluoroethyl groups attached as side chains of

Table 1
The particle size data.

Polymer	Particle Size (nm)[a]	pCMC (−log (M) ± SD)[b]
$M1(F2Ox)_{3-4}$	4.35 ± 1.00	5.014 ± 0.03
$M1(F2Ox)_{4-5}$	15.74 ± 0.631	4.770 ± 0.03
$M5(F2Ox)_{3-5}$	4.51 ± 0.753	4.995 ± 0.08
$M5(F2Ox)_{7-9}$	15.61 ± 0.322	N/A

[a] Particle sizes of fluoropolymer-based aggregates. Data are given with the standard deviation (n = 3). Each measurement was repeated three times.
[b] Critical micelle concentration determined by surface tension. Each measurement repeated four times. CMC of $M5(F2OX)_{7-9}$ was not determined due to insufficient yields of this polymer fraction.

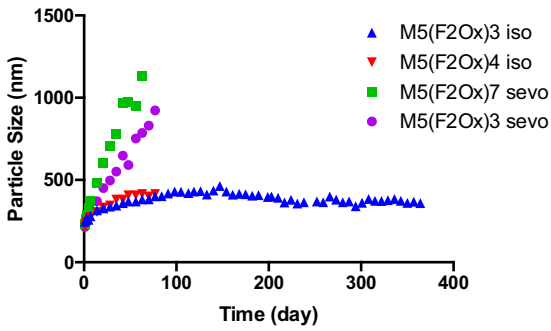


Fig. 2. Change in particle sizes of fluoropolymer-based emulsions with time: (green) $M5(F2Ox)_7$ with sevoflurane; (purple) $M5(F2Ox)_3$ with sevoflurane; (blue) $M5(F2Ox)_3$ with isoflurane, (red) $M5(F2Ox)_4$ with isoflurane. All emulsions contained 20% of respective fluorous anesthetic and 10% perfluorooctyl bromide (a stabilizing additive) [8,9] and were prepared in saline (0.9% w/w NaCl). Note standard error bars are removed for clarity. They are available in the Supporting information. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

hydrophobic monomers led to a significant difference in stability between sevoflurane and isoflurane emulsions, the latter being remarkably more stable. The main mechanism of destabilization of fluorocarbon-based emulsions is molecular diffusion, better known as Ostwald ripening [21]. In this mechanism, individual molecules of fluorous anesthetic diffuse out of smaller particles, due to the higher curvature of these particles and therefore higher chemical potential, to join larger growing droplets. The rate of increase of the droplets' volume over time is a linear function of the interfacial tension, the solubility and diffusion of the dispersed perfluorocarbon in the aqueous phase, and the particle radius [21]. Plotting particle size *vs.* time gives a fair representation of emulsion stability. For practical use, IV injectable emulsions must maintain a mean diameter $\leq$500 nm within an 11-month period when stored at 5 °C [10].

Fig. 2 shows the ripening behavior with time of emulsions of sevoflurane and isoflurane made with the polymer containing either 3, 4, or 7 units of the perfluoroether telomer. While the sevoflurane emulsion showed a quick increase in particle size and eventual phase-separation, isoflurane led to a much more stable formulation containing 20% v/v of anesthetic, with particle size staying around 400 nm for over a year. Polymers with longer fractions of polyoxetane were poorly water-soluble and thus unable to make sevoflurane or isoflurane emulsions.

The variation of particle size between the emulsions of polymer $M5(F2Ox)_3$ can be explained when considering the chemical structure of both polymer and fluorous anesthetic. Sevoflurane has a greater fluorine content than isoflurane and will be solubilized better by a fully fluorophilic chain. The hydrophobic chain used in these polymers contains a short perfluoroethyl group, as well as a polyether backbone, giving the polymer both lipophilic and fluorophilic properties. Therefore, we ascribe the difference in stability between the two emulsions to a better match between the hydrophobicity/fluorophilicity balance of the polymer with that of isoflurane.

3. Conclusions

In summary, we have synthesized amphiphilic diblock copolymers where a methoxy-PEG is attached to a short block with a hydrophobic backbone and perfluoroethyl side chains. The size of the hydrophobic/fluorophilic moiety affected surface properties such as critical micelle concentration, hydrophobic drug encapsulation and nanoemulsion stability. It was found that the short pendant perfluoroethyl side chain induced a balance of

hydrophobicity and fluorophilicity optimal for emulsification of isoflurane. In contrast, the more fluorophilic sevoflurane formed unstable emulsions and the encapsulation of purely hydrophobic molecules was not possible at therapeutic concentrations, confirming the mixed lipophilic/fluorophilic environment provided by the perfluoro telomer block.

Highly concentrated, 20% v/v emulsions of isoflurane were possible with the polymer containing up to three or four units of perfluoroether telomer. The emulsions were found to be stable over a period of 12 months.

These results indicate that fluorophilic behavior can be induced using short, perfluoroethyl groups. Potential metabolism products of such short fluorocarbons do not bioaccumulate [3,4] and therefore toxicity considerations will not be a limiting factor for their application.

4. Experimental

4.1. Materials

Paclitaxel was purchased from LC Laboratories. Isoflurane was purchased from Piramel Healthcare. Sevoflurane was purchased from Abbott Labs and normal saline (AirLife sterile 0.9% NaCl for irrigation USP) from Braun Medical Inc. Fluorous alcohols and perfluorooctyl bromide were purchased from SynQuest. All other reagents and solvents were of ACS grade or higher, were purchased from Sigma-Aldrich, and were used as received, unless otherwise specified.

4.2. Instrumentation and methods

^{1}H, ^{13}C and ^{19}F NMR experiments were conducted on a Varian *UNITY INOVA*-400 NMR spectrometer at 25 °C using deuterochloroform ($CDCl_3$) as the solvent with TMS as an internal reference.

Surfactants were purified by automated flash chromatography using a CombiFlash® Rf 4x system equipped with ELSD for compound visualization and a REDI-Sep Rf Gold C-18 silica high-performance aqueous reverse phase cartridge. Products were eluted with a 10–100% methanol in water (0.1% formic acid) gradient.

4.3. Synthesis of 3-bromo-2-bromomethyl-2-methylpropyl acetate (**2**)

1,1,1-Tris(hydroxymethyl)ethane (TME) (25.58 g, 212.9 mmol) was weighed into a 500 mL round bottom flask and glacial acetic acid (100 mL) was added, stirring vigorously for 2 h to partially dissolve TME. Sodium bromide (65.75 g, 638.97 mmol) was added and reaction fitted with addition funnel and flushed with argon. Sulfuric acid (25 mL, 511 mmol) was added drop wise over 1 h, and the flask fitted with condenser and heated to 110 °C. After 7 days, heat was turned off and reaction came to room temperature. The reaction was then diluted with 250 mL water and layers separated. Organic layer was washed with water (100 mL), 0.5 M sodium hydroxide (2 × 200 mL), and brine (200 mL). The reaction was then dried over anhydrous magnesium sulfate and filtered. Crude oil was purified by flash column, packing with hexane and eluting with 5% ethyl acetate/hexane to collect first product only. Oil was isolated by rotary evaporation to give 58.42 g (95% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.06 (s, 2H), 3.45 (dd, J = 12.8, 10.4 Hz, 4H), 2.08 (s, 3H), 1.17 (s, 3H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 67.3, 39.2, 38.5, 34.7, 31.8, 25.5, 22.9, 21.0, 20.4, 14.3.

4.4. Synthesis of 3-(bromomethyl)-3-methyloxetane (**3**)

3-Bromo-2-bromomethyl-2-methylpropyl acetate (20.13 g, 69.92 mmol) was dissolved in dichloromethane (100 mL) and 3 M sodium hydroxide (100 mL). Tetrabutylammonium bromide (1.32 g, 4.09 mmol) was added and reaction stirred vigorously under argon and heated to reflux. After 24 h, reaction was stopped and layers were separated. Dichloromethane was gently removed under reduced pressure. Oil was purified by vacuum distillation, collecting fraction at 50 °C to give 5.07 g (43.9%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.38 (d, J = 6.4 Hz, 2H), 4.33 (d, J = 6.4 Hz, 2 H), 3.59 (s, 2 H), 1.37 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ 80.74, 41.63 (2C), 40.79, 22.62.

4.5. Synthesis of 3-(1H,1H-perfluoropropan-1-oxymethyl)-3-methyloxetane (**4**)

3-(Bromomethyl)-3-methyloxetane (5.07 g, 30.76 mmol), pentafluoropropan-1-ol (4.73 g, 31.49 mmol), tetrabutylammonium bromide (246.3 mg, 0.764 mmol) and water (4.5 mL) were added to a 100 mL round-bottom flask with stir bar, flask flushed with argon and heated to 95 °C. Potassium hydroxide (4.36 g, 40% solution in water) was added over 10 min to the stirring reaction at 95 °C. Reaction was left overnight under argon. Mixture was then allowed to cool to room temperature and dichloromethane (12 mL) was added and layers separated. The aqueous layer was extracted with dichloromethane (20 mL). Combined organic layers were dried over anhydrous magnesium sulfate and the solvent gently removed by rotary evaporation. The remaining oil was purified by vacuum distillation, collection fractions at 20 °C to yield 1.05 g (57% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 4.49 (d, J = 6 Hz, 2 H), 4.37 (d, J = 6 Hz, 2 H), 3.96 (tq, J = 12, 1.2 Hz, 2 H), 3.69 (s, 2 H) 1.32 (s, 3 H). ^{13}C NMR (100 MHz, $CDCl_3$): 79.83, 78.32, 68.24 (t, J = 26.8 Hz), 40.15, 21.11. Carbons containing F's were not visible with the used acquisition scans. ^{19}F NMR (376 MHz, $CDCl_3$): −84.01 (s, 3F), −123.59 (t, J = 12.4 Hz, 2F).

4.6. Synthesis of M1(F2Ox)$_n$ (**5-1**)

Monomethoxy polyethylene glycol (430 mg, average molecular weight = 880 g/mol) was dissolved in 7 mL anhydrous dichloromethane. Boron trifluoride–diethyl ether complex (75 μL) was added under argon and the mixture was allowed to stir for 30 min. Solution was then cooled in and ice bath and fluorous oxetane **4** (1.00 g) dissolved in dichloromethane was added drop wise over the course of 30 min. The reaction was stirred under argon overnight and brought to room temperature. Reaction was then quenched with water and diluted with water (5 mL) and brine (5 mL) to break up emulsion. Layers were separated and the aqueous layer was extracted with dichloromethane (2 × 5 mL). Organic layers were combined and dried over anhydrous magnesium sulfate and filtered. The solvent was removed under low pressure and the residue was purified by reverse-phase flash chromatography to yield 563 mg (64% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (t, J = 12.8 Hz, 34 H), 3.65 (m, 80 H), 3.43 (m, 20 H), 3.37 (m, 11 H), 3.18 (m, 50 H), 0.90 (m, 46 H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −84.07 (m, 3F), −123.84 (m, 2F).

4.7. Synthesis of M5(F2Ox)$_n$ (**5-2**)

Monomethoxy polyethylene glycol (2.24 g, average molecular weight = 4200 g/mol) was dissolved in 7 mL anhydrous dichloromethane. Boron trifluoride–diethyl ether complex (55 μL) was added under argon and the mixture was allowed to stir for 30 min. Solution was then cooled in and ice bath and fluorous oxetane **4** (1.05 g) in dichloromethane solution was added drop wise over the course of 30 min. The reaction was stirred under argon overnight and brought to room temperature. Reaction was then quenched with water, diluted with water (5 mL) and brine (5 mL) to break up emulsion. Layers were separated and the aqueous layer was

extracted with dichloromethane (2 × 5 mL). Organic layers were combined and dried over anhydrous magnesium sulfate and filtered. The solvent was removed under low pressure. Polymer was purified by reverse-phase flash chromatography to yield 1.408 g (55% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.84 (t, J = 12.8 Hz, 79 H), 3.65 (m, 480 H), 3.43 (m, 41 H), 3.37 (m, 30 H), 3.18 (m, 124 H), 0.90 (m, 108 H). ^{19}F NMR (376 MHz, $CDCl_3$): δ −84.07 (m, 3F), −123.84 (m, 2F).

4.8. Micelle preparation—solvent evaporation method (SEM)

Polymer is dissolved in methanol or acetonitrile to a desired concentration. Polymer solution and additive (*e.g.*, paclitaxel in acetonitrile) are added to a 25 mL round bottom flask and rotated for 5 min at 60 °C on a rotary evaporator, no vacuum, and then the solvent was removed in vacuo with rotation for 15 min. The film was then dispersed with Millipore water heated to 60 °C and filtered with a 0.45-μm nylon filter.

4.9. Preparation of fluorous anesthetic nanoemulsions

Polymer solution in normal saline solution (10 mM, 11.9 mL) was prepared freshly. Normal saline was made with 0.9% (w/w) of sodium chloride.

Sevoflurane or isoflurane (3.4 mL) and perfluorooctyl bromide (1.7 mL) were added to the polymer solution, for a total volume of 17 mL. The homogenizer and microfluidizer were previously cleaned with 70% and 100% ethanol, followed by 70% and 100% methanol, and finally with three rinses of Millipore water to remove any solvents from previous washes. Once prepared the mixture is then homogenized with the high-speed homogenizer (Power Gen 500, Fisher Scientific, Hampton, NH) for 1 min at 21000 rpm at room temperature. The crude emulsion made with the high speed homogenizer was further homogenized with a Microfludizer (model 110 S, Microfluidics Corp., Newton, MA) for 1 min under 5000 psi with the cooling bath kept at 15 °C. The final emulsion was then filtered with a 0.45 μm nylon filter and stored in plastic centrifuge tubes (Corning Inc., Corning, NY) at 4 °C.

4.10. Particle size determination by dynamic light scattering (DLS)

Particle sizes of polymeric micelles were analyzed by dynamic light scattering (Zetasizer Nano-ZS, Malvern Instruments, Worcestershire, UK). The polymer solution was measured directly without dilution and analyzed. Each particle size analysis was run at room temperature and repeated in triplicate with the number of scans of each run determined automatically by the instrument according to the concentration of the solution. The data was analyzed using Malvern software analysis and reported as volume weighted average diameters.

Particle sizes of emulsions were analyzed by dynamic light scattering (NICOMP 380ZLS, Particle Sizing Systems, Santa Barbara, CA). The emulsions were diluted at the intensity factor of 300 by adding 60 μL of the emulsion to 2.940 mL of Millipore water. Each particle size analyzing was run for 5 min at room temperature and repeated three times. The data was analyzed using Gaussian analysis and reported as volume weighted average diameters.

4.11. Critical micelle concentration (CMC) determination—surface tensiometry

Polymer was dissolved in Millipore water to a concentration of 1 mM and concentrations down to 1 nm were prepared by serial dilution and transferred to 20 mL disposable scintillation vials. After solutions were made, the samples were vortexed and sonicated and then heated in a water bath at 40 °C for 2–3 h. Solutions were then allowed to equilibrate for 24 h. Surface tensions were measured on a KSV sigma 701 tensiometer (KSV Instruments, Helsinki, Finland) equipped with a Julabo F12-MC circulator for constant temperature control. Custom round rod made of platinum with a diameter of 1.034 nm with wetted length of 3.248 mm was used. First, the rod was submerged into absolute alcohol and flame dried with a Bunsen burner for 4 s, then repeated after 4 min and hung on instrument and allowed to cool to room temperature without touching any surface. Before running the experimental samples, the surface tension of Millipore water was measured as control to confirm vial and rod were fully cleaned and surface tension was within 1 of 78.2 mN/m. The surface tension measurements began with the least concentrated solution and proceed to successively more concentrated solutions. The surface tension at each concentration was measured in quadruplet and average recorded. The critical micelle concentration value was determined from crossover point of two lines: the baseline of minimal surface tension and the slope where surface tension showed linear decline; error determined by weighted least squares analysis .

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2016.09.001.

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