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Reverse aqueous emulsions and microemulsions in HFA227 propellant stabilized by non-ionic ethoxylated amphiphiles

Udayan Chokshi[c], Parthiban Selvam[c], Lionel Porcar[a,b], Sandro R.P. da Rocha[c,*]

[a] Materials Science and Engineering Department, University of Maryland, College Park, MD 20742, United States
[b] Centre for Neutron Research, National Institute for Standards and Technology, 100 Bureau Drive, Bldg. 235, Stop 8562, Gaithersburg, MD 20899, United States
[c] Department of Chemical Engineering and Materials Science, Wayne State University, 5050 Anthony Wayne Dr., Detroit, MI 48202, United States

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ABSTRACT

In this work we use *in situ* high-pressure tensiometry to screen non-ionic ethoxylated surfactants at the 1,1,1,2,3,3,3-heptafluoropropane (HFA227) propellant|Water (HFA227|W) interface. The $EO_nPO_{\sim 30}EO_n$ series, where *EO* stands for ethylene oxide and *PO* for propylene oxide, and *n* the number of repeat *EO* units, was selected for this study based on the favorable interactions reported between HFA propellants and the *PO* moiety. The surfactants used in FDA-approved pressurized metered-dose inhaler formulations were also investigated. Tension measurements provide not only information on the relative activity of the different surfactants in the series, but they also serve as a guide for selecting an appropriate candidate for the formation of reverse aggregates based on the surfactant natural curvature. Moreover, the effect of ethanol and the chemistry of the surfactant tail group on the surfactant activity were also investigated. Surfactants with hydrogenated tails are not capable of forming stable water-in-HFA227 microemulsions. This is true even at very low tensions observed when in the presence of ethanol, indicating the lack of affinity between HFA227 and hydrogenated moieties—the surfactant does not tend to curve about water. On the other hand, *PO*-based amphiphiles can significantly reduce the tension of the HFA227|W interface. Small angle neutron scattering (SANS) and UV–vis spectroscopy results also reveal that a selected ethoxylated amphiphile ($EO_{13}PO_{30}EO_{13}$ at 1 mM concentration), when in the presence of ethanol, is capable of forming stable cylindrical reverse aqueous microemulsions. $EO_{13}PO_{30}EO_{13}$ is also capable of forming emulsions of water-in-HFA227 that are fairly stable against coalescence. Such dispersions are potential candidates for the delivery of small polar solutes and larger therapeutic biomolecules to and through the lungs in the form of pMDI formulations, and in other medical sprays.

1. Introduction

The inhalation route has been traditionally used for delivering drugs that exert their therapeutic effect locally; i.e., in the lungs (Courrier et al., 2002). However, the large alveolar surface area, reduced thickness of the epithelial barrier, extensive vascularization, and relatively low proteolytic activity (Patton and Byron, 2007) also make the lungs an outstanding route for the delivery of therapeutics to the systemic circulation (Laube Beth, 2005; Owens et al., 2003). Within this context, there is a need for the development of novel inhalation formulations that can be used for the systemic delivery of both small molecular weight drugs and larger therapeutic biomolecules.

The most economical vehicles for the oral delivery of drugs to the respiratory tract are the pressurized metered-dose inhalers (pMDIs) (Bowman and Greenleaf, 1999; McDonald and Martin, 2000; Tarara et al., 2004). pMDIs use a propellant to expel the pharmaceutical product as an aerosol (Meakin et al., 2003). The propellant also works as the solvent medium where the drugs are either dispersed or solubilized. For environmental reasons, the hydrofluoralkanes (HFAs) (Chinet, 2000; Tansey, 1997) more specifically 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227), have replaced the chlorofluorocarbon (CFC) propellants in pMDI formulations (McDonald and Martin, 2000). HFAs have been selected partly because of their exceptional inertness (McDonald and Martin, 2000). HFAs are also biocompatible, and non-ozone depleting (Alexander and Libretto, 1995; Emmen et al., 2000; Graepel and Alexander, 1991). However, due to differences in physicochemical characteristics compared to those of CFCs (Butz et al., 2002), most notably their higher polarity, the reformulation of pMDIs with HFAs has been a challenging

* Corresponding author. Tel.: +1 313 577 4669; fax: +1 313 578 5820.
E-mail address: sdr@eng.wayne.edu (S.R.P. da Rocha).

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task (Wu et al., 2007c). A concerted effort is currently under way to understand the solvation properties of HFAs, and the characteristics of colloidal domains in such low dielectric propellant media that should aid not only in the reformulation of existing pMDIs but also in the design of novel HFA-based formulations (Peguin and da Rocha, 2008; Peguin et al., 2007; Selvam et al., 2008; Wu et al., 2007b, 2007c).

pMDIs can be formulated either as solution (drug is soluble in the propellant), or suspension (drug particles dispersed in the propellant) formulations. In general, polar therapeutics have low solubility in HFAs (Patton et al., 2004; Rau, 2005) and thus have to be formulated as dispersions, or as solutions with the aid of a co-solvent (Rogueda, 2005; Tarara et al., 2004). Suspension formulations, which correspond to approximately 50% of the commercially available pMDIs (Rogueda, 2005; Stefely, 2002), typically contain a surfactant to aid in the dispersion of the drug particles (Stefely, 2002; Stefely et al., 2000; Wu and da Rocha, 2007), and a co-solvent used to enhance the solubility of the amphiphile (Steckel and Muller, 1998; Vervaet and Byron, 1999). Several studies have been published in recent years addressing the design of surfactants with enhanced solubility in HFAs (Selvam et al., 2008; Stefely, 2002; Wu et al., 2007b, 2008; Wu and da Rocha, 2007), thus potentially avoiding the use of co-solvents in pMDI formulations (Rogueda, 2005; Wu et al., 2008). New particle (solid-based) engineering technologies that do not rely on the use of surfactants in solution have also been proposed (Dellamary et al., 2000; Edwards et al., 1997; Wu et al., 2007a, 2007c), some of which lend themselves to the formulation of therapeutic biomolecules (Rogueda, 2005; Wu et al., 2007a, 2007c).

Aqueous-based dispersions in the form of reverse emulsions (Butz et al., 2002; Krafft, 2001) and microemulsions (Meakin et al., 2003; Patel et al., 2003a, 2003b; Selvam et al., 2006, 2008; Sommerville and Hickey, 1998; Sommerville et al., 2000, 2002) have been previously suggested as an alternative way to formulate therapeutic biomolecules or small polar drugs that are not soluble in HFA propellants. Water-in-perfluorooctyl bromide (W/PFOB) emulsions stabilized with a fluorinated surfactant have been shown to be easily dispersible in both HFA134a and HFA227 (Butz et al., 2002). The external phase (in that particular study) is a combination of the propellant HFA and PFOB, which (the latter) may be acting as a co-solvent to the fluorinated surfactant. The study with the W/PFOB in HFAs is also relevant in that it demonstrates that various drugs, including antibiotics, vasodilators and anticancer agents can be incorporated in the aqueous phase of the W/PFOB emulsion, and thus potentially dispersed in propellant HFA (Sadtler et al., 1999). Thermodynamically stable water-in-HFA (W/HFA) microemulsions are another potential pseudo-solution formulation (Meakin et al., 2003; Patel et al., 2003a, 2003b; Selvam et al., 2008; Steytler et al., 2003), where water-soluble therapeutics could be formulated. We have recently shown that ethoxylated surfactants are capable of forming stable aqueous reverse aggregates in HFA134a (Selvam et al., 2008). Small angle neutron scattering spectra (SANS) indicated the formation of aggregates with a cylindrical geometry, and containing a water core radius of 12–14 and 50–95 Å in length. The uptake of a model biomolecule within the core of the aggregates was demonstrated, illustrating the potential applicability of such formulations (Selvam et al., 2008).

The objective of this work was to investigate the behavior of ethoxylated surfactants at the HFA227–water (HFA227|W) interface, and their ability to form reverse aqueous aggregates in HFA227 in the form of emulsions and microemulsions. We employed a combination of experimental techniques including *in situ* high-pressure tensiometry, molecular probe UV–vis spectroscopy small angle neutron scattering (SANS), and visual inspection of the contents of the pressure cells to probe the activity, structure and stability of the reverse aggregates. The relevance of this work stems from the fact that such dispersions in HFA propellants are potential formulations for the delivery of small and large polar therapeutics to and through the lungs. The results shown here are also of relevance to traditional solution and dispersion pMDI formulations where surfactants are generally required excipients (Blondino, 1995). Previous studies indicate significant differences in the behavior of colloidal dispersions in HFA134a and HFA227. For example, water in fluorocarbon emulsions was more stable in HFA227 than in HFA134a (Butz et al., 2002). Generally, non-ionic surfactants show higher solubility in HFA227 than compared to HFA134a due to stronger interactions between the surfactant and HFA227 (Peguin and da Rocha, 2008; Ridder et al., 2005), and this may also affect the stability of both solid and aqueous dispersions in the different propellant HFAs. This study will also help understand differences in how ethoxylated surfactants behave at the interface between water and these propellant HFAs (HFA134a and HFA227).

2. Materials and methods

2.1. Materials

2H,3H-perfluoropentane (HPFP, assay 98% min) was purchased from SynQuest labs Inc. HFA227 (assay 99.9%) was a gift from Solvay Fluor und Derivative GmbH & Co. KG. Acetone and ethanol (analytical grade) were purchased from Fischer Scientific. Pluronic L® surfactants with a general structure (ethylene oxide)–(propylene oxide)–(ethylene oxide) ($EO_nPO_mEO_n$, where m and n are the average number of repeat units) were a gift from BASF. Sorbitan trioleate (Span 85, >99%) was purchased from TCI America Inc. Poly(ethylene glycol) (300 g mol^{-1}) (PEG300) and poly(propylene glycol) (2000 g mol^{-1}) (PPG2000) were purchased from Acros Organics. Lecithin (refined, 100%) was purchased from Alfa Aesar. Oleic acid (>99%) was purchased from Sigma–Aldrich. All of the surfactants were used as received. Ethanol (100%) was purchased from AAPER Alcohol and Chemical Co., and methyl orange [$(CH_3)_2NC_6H_4N{=}NC_6H_4SO_3{\cdot}Na^+$, dye content, 95%] was purchased from Sigma–Aldrich. Deionised water (Nanopure: Barnstead) with surface tension of 73 mN m^{-1} at 295 K was used in all experiments. Pressure proof glass vials (68000318) were a gift from West Pharmaceutical Services. The metering valves (EPDM Spraymiser^{TM}, 50 μl) were a gift from 3 M Inc.

2.2. High-pressure tensiometry

A variable volume pendant drop tensiometer was used to measure the interfacial tension of the HFA227|water (HFA227|W) interface with or without the presence of interfacially active species. The instrument, which allows us to measure the tension at high pressures, was described in detail in a previous publication (Peguin et al., 2006). A very small droplet of water (~3–5 μl) was initially formed into HFA227 (3.3 ml), and allowed to equilibrate in the presence of surfactant. On average, three such droplets were formed for each measurement, in a way that the depletion on surfactant concentration from bulk HFA227 was minimized. Once the system is equilibrated, a droplet of water (or HFA227) was injected into a high-pressure cell as a pendant drop (hanging drop), in an HFA277 (aqueous) surfactant solution. Visual ports in the pressure cell allowed for the extraction of the droplet profile at 298 K and saturation pressure of the system. The reported values are averages of at least three independent measurements. The whole droplet profile was used to determine the γ with the Laplace equation (KSV, 2001).