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Reverse aqueous microemulsions in hydrofluoroalkane propellants and their aerosol characteristics

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ABSTRACT

In this work we describe the structure and environment of reverse aqueous microemulsions formed in 1,1,1,2-tetrafluoroethane (HFA134a) propellant in the presence of a non-ionic ethoxylated copolymer, and the aerosol characteristics of the corresponding pressurized metered dose inhaler (pMDI) formulations. The activity of selected polypropylene oxide–polyethylene oxide–polypropylene oxide ($PO_mEO_nPO_m$) amphiphiles at the HFA134a–water interface was studied using *in situ* high-pressure tensiometry, and those results were used as a guide in the selection of the most appropriate candidate surfactant for the formation of microemulsions in the compressed HFA134a. The environment and structure of the aggregates formed with the selected surfactant candidate, $PO_{22}EO_{14}PO_{22}$, was probed via UV–vis spectroscopy (molecular probe), and small angle neutron scattering (SANS), respectively. High water loading capacity in the core of the nanoaggregates was achieved in the presence of ethanol. At a water-to-surfactant molar ratio of 21 and 10% ethanol, cylindrical aggregates with a radius of 18 Å, and length of 254 Å were confirmed with SANS. Anderson Cascade Impactor (ACI) results reveal that the concentration of the excipients (C_{exp}, including surfactant, water and ethanol) has a strong effect on the aerosol characteristics of the formulations, including the respirable fraction, and the mass mean aerodynamic diameter (MMAD), and that the trend in MMAD can be predicted as a function of the C_{exp} following similar correlations to those proposed to common non-volatile excipients, indicating that the nanodroplets of water dispersed in the propellant behave similarly to molecularly solubilized compounds. Cytotoxicity studies of $PO_{22}EO_{14}PO_{22}$ were performed in A549 cells, an alveolar type II epithelial cell line, and indicate that, within the concentration range of interest, the surfactant in question decreases cell viability only lightly. The relevance of this work stems from the fact that aqueous-based HFA-pMDIs are expected to be versatile formulations, with the ability to carry a range of medically relevant hydrophilic compounds within the nanocontainers, including high potency drugs, drug combinations and biomacromolecules.
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1. Introduction

Aqueous reverse microemulsions in propellant-based inhalers have been suggested as a possible vehicle for the delivery of polar drugs, including biomolecules, to and through the lungs (Patton and Byron, 2007; Rogueda, 2005; Courrier et al., 2002; Williams and Liu, 1999; Blondino, 1995; Selvam et al., 2008; Bharatwaj et al., 2010; Wu et al., 2008). Encapsulation and delivery of polar drugs in reverse aqueous microemulsions seems to be not only viable, but also very attractive, given the advantages of portable inhalers such as pMDIs (Selvam et al., 2008; Meakin et al., 2006; Steytler et al., 2003; Patel et al., 2003a,b; Peguin et al., 2006; Chokshi et al., 2009) The strategy is very simple, and consists in solubilizing the therapeutic of interest within the core of the nano-sized aqueous reverse aggregates stabilized by surfactant molecules, which are homogeneously dispersed in the propellant (Selvam et al., 2008; Wu et al., 2008; Meakin et al., 2006; Chokshi et al., 2009; Butz et al., 2002). This approach may also have some potential advantages over traditional dispersion-based (micronized drugs) pMDI formulations. For example in the case of high potency therapeutics, where drug losses due to interactions between the crystals and the canister walls may compromise the reliability of the dosage, as the total drug surface area may approach that of the walls of the container (Traini et al., 2005, 2006). This problem is expected to be mitigated by formulating the drug within the microemulsion core. Microemulsions could also be amenable to the formulation of combination therapies.

However, very few studies have reported the formulation of reverse microemulsions in propellants in general (Sommerville and

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Hickey, 2003; Sommerville et al., 2000; Courrier et al., 2004), and even fewer studies have addressed microemulsions in hydrofluoroalkanes (HFAs) (Selvam et al., 2008; Meakin et al., 2006; Steytler et al., 2003; Patel et al., 2003a,b; Chokshi et al., 2009), which are the only propellants accepted by the FDA for use in pMDIs. Within those studies that discuss microemulsions in HFA-based pMDIs, most are related to fluorinated surfactants (Steytler et al., 2003; Patel et al., 2003a,b), which are less appealing to pulmonary drug delivery applications (Lawrence and Rees, 2000). It is also worth mentioning that no study has previously addressed the aerosol characteristics of HFA-based microemulsion formulations in pMDIs. Some factors that contribute to the scarcity of studies in this area include the fact that the experiments need to be performed under pressure (Rogueda, 2005; Blondino, 1995; Peguin et al., 2006; Vervaet and Byron, 1999; Farr et al., 1987; Ridder et al., 2005; Selvam et al., 2006). The need for highly interfacially active species to facilitate the formation of such aggregates (Rogueda, 2005; Peguin et al., 2006; Vervaet and Byron, 1999; Ridder et al., 2005; Blondino and Byron, 1998; Wu et al., 2007a,b; Peguin and da Rocha, 2008; Peguin et al., 2009) has also created difficulties in the development of microemulsion-based pMDIs. In that aspect, the challenges in developing reverse-aggregate-based formulations are similar to those that exist in the design of particle-based dispersions in HFAs, where excipients containing well-solvated stabilizing moieties are required. However, solvation in HFAs, and the concept of HFA-philicity is just beginning to be understood (Rogueda, 2005; Williams and Liu, 1999; Lawrence and Rees, 2000; Vervaet and Byron, 1999; Ridder et al., 2005; Selvam et al., 2006; Peguin and da Rocha, 2008).

Based on this rationale, we report here the ability of an ethoxylated non-ionic amphiphile to form aqueous reverse aggregates in HFA134a in the presence of a water-soluble model solute, methyl orange (MO), and the effect of the reverse aggregates and other excipients on the aerosol characteristics of the corresponding formulations. The design and characterization of the microemulsions was approached rationally, through *in situ* high-pressure tensiometry, UV–vis spectroscopy, and small angle neutron scattering (SANS) experiments. The effect of non-volatiles on the aerosol characteristics were investigated via inertial impaction (Anderson Cascade Impactor, ACI). The cytotoxicity of a selected ethoxylated surfactant capable of forming water-in-HFA (W/HFA) microemulsions was studied on the A549 (alveolar type II epithelial) cell line. This work is relevant in that it demonstrates the potential of reverse-aqueous aggregates in HFAs as pMDI formulations for the non-invasive delivery of water-soluble therapeutics to and through the lungs, with particular potential relevance to high potency therapeutics, biologicals and drug combinations.

2. Materials and methods

2.1. Materials

Pluronic R® surfactants, with the general structure $PO_mEO_nPO_m$ (EO = ethylene oxide; PO = propylene oxide; m, n = average number of repeat units) were kindly donated by BASF. The surfactants were used as received. Deionized water (NANOpureII; Barnstead), with a resistivity of 18.2 MΩ cm^{-1}, was used in all experiments. Commercial (Pharma grade) HFA134a (>99.99%) was a gift from Solvay Fluor & Derivate GmbH (Hanover, Germany). Ethanol (100%) was purchased from AAPER Alcohol and Chemical Co. Methyl orange [$(CH_3)_2NC_6H_4N{=}NC_6H_4SO_3{\cdot}Na^+$, dye content – 95%] was purchased from Sigma–Aldrich. The A549 cell line was from ATCC. RPMI 1640 supplemented with L-glutamine was purchased from Invitrogen. The RPMI 1640 medium was supplemented with 10% FBS and 100 μg ml^{-1} penicillin and streptomycin, both purchased from Sigma (St. Louis, MO). Culture flasks (75 cm^2, BD Falcon) and 96-well culture plates were purchased from VWR. MTS [3-(4,5-dimethylthiazole-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H, tetrazolium, inner salt] was purchased from Promega. Pressure proof glass vials (68000318) were purchased from West Pharmaceutical Services. The metering valves (EPDM Spraymiser™, 50 μl) were a gift from 3M Inc. The actuators used in all experiment were the same ones as those for the commercial Ventolin HFA® formulation.

2.2. Surfactant activity

The interfacial tension (γ) measurements were performed in a high-pressure pendant drop tensiometer as described previously (Peguin et al., 2006). Briefly, a droplet of water (or HFA134a) was injected into a high-pressure cell, in an HFA134a (aqueous) surfactant solution. Visual ports allowed for the extraction of the droplet profile. Measurements were made at 298 K and saturation pressure of the propellant mixture. The whole droplet profile was used to determine the γ with the Laplace equation (Peguin et al., 2006). After the injection of each drop, several snapshots were taken with time, until equilibration. The reported results are averages of at least three independent measurements.

2.3. Probing the environment of the reverse aggregates

In situ UV–vis spectra of HFA134a containing one or more of the following: surfactant, water, a probe, and ethanol, were obtained as described previously (Selvam et al., 2008). A known amount of surfactant (typically greater than the critical aggregation concentration) and a known volume of an aqueous solution of the solvatochromic probe MO was added to the saturated mixture in a 15 ml high-pressure glass vial (Chemglass). HFA134a or HFA134a–ethanol mixture saturated with pure water in an 'HFA saturation cell' was then added to the high pressure glass vial. Since microemulsion formation is a thermodynamically stable process; microemulsions will (spontaneously) form pseudo-solutions that are transparent due to their small (several nanometers) size. The presence and nature/structure of the microemulsions is confirmed/analyzed using UV–vis spectroscopy. After equilibration, the contents of the cell were transferred to a home-made spectroscopic high-pressure cell fitted with two sapphire windows (1 cm path length). The spectra were obtained with a Varian UV–vis spectrophotometer (Cary 3E®). The baseline for this system was obtained from the spectrum of an aqueous-saturated HFA134a or HFA134a–ethanol solution equilibrated with MO. The corrected water-to-surfactant molar ratio (W_o) was thus directly assessed; i.e., there was no need to rely on calculated water solubility in HFA since the HFA134a or HFA134a–ethanol mixture was pre-equilibrated (saturated) with water, thus allowing for the reporting of accurate water loadings.

2.4. Microstructure of the reverse aggregates

High-pressure SANS experiments in HFA134a were performed on the NG7 30-m SANS instrument at NIST (Center for Neutron Research in Gaithersburg, MD). Neutrons of wavelength $\lambda = 6$ Å with a distribution of $\Delta\lambda/\lambda = 11\%$ were incident on samples held in a custom-built high-pressure SANS cell. Sample to detector distances between 3 and 15 m were used to give a q range of $0.0035\ \text{Å}^{-1} < q < 0.45\ \text{Å}^{-1}$, where $q = (4\pi/\lambda)\sin(\theta/2)$ is the magnitude of the scattering vector. Sample scattering intensity was corrected for background, empty cell scattering and detector sensitivity. Corrected data sets were circularly averaged, placed on an absolute scale and analyzed using Igor Pro (Kline, 2006). The scattering length densities (SLD) were obtained from the

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