Drug delivery to and through the lungs using pressurized metered dose inhalers (pMDIs) are of increasing relevance. pMDI-based formulations are potential candidates for the delivery of pharmaceutically relevant biomolecules including peptides, DNA and proteins. However, polar molecules - including water, have very low solubility in the propellants acceptable for use in pMDIs. The development of novel pMDI-based formulations for the delivery of hydrophilic substances has been also challenged by the resolution of the Montreal Protocol, which enforces the replacement of CFCs with the more environmentally friendly, non-ozone depleting hydrofluoroalkanes (HFAs). In spite of the fact that the operation of pMDIs with HFAs is similar to those with CFCs, previous formulations are not compatible due to the significantly different properties between these two classes of fluids. For example, none of the FDA approved surfactants commonly used in CFC formulations are soluble in HFAs. Difficulties in studying the fundamental interfacial properties of volatile propellant mixtures such as surface/interfacial tension and micellization behavior have hindered the design of appropriate surfactants for HFAs.

In this work, we report the in-situ (high-pressure) tensiometric results for the bare and surfactant-modified HFA-Water (HFA|W) interface. Reverse aqueous aggregates dispersed in HFAs can be utilized for the delivery of biomolecules and other polar drugs. Despite its low solubility in HFAs, it is found that alkyl-based amphiphiles are capable of reducing the tension of the pressurized HFA-134a|W interface by as much as 24.5 mN/m. Replacement of the alkyl moiety with a tail containing polar sites is shown to enhance the interfacial activity of the amphiphile, as indicated by a lower interfacial tension of the modified interface. Optimum surfactant balance is investigated by determining the interfacial tension of the surfactant modified HFA|W interface as the hydrophilic-HFA philic balance (HFB) is varied systematically. Diagrams of tension vs. HFB also allow us to determine the favored natural curvature that would be assumed for those amphiphiles capable of forming reverse aqueous aggregates in HFAs. The ability of the model propellant 2H, 3H perfluoropentane (HPFP) to mimic pressurized HFA propellants is also discussed.