577g Microscopic Approach for the Design of Surfactants for Pmdi-Based Formulations: Ab Initio Calculations and Chemical Force Microscopy

Robson S. Peguin, Libo Wu, and Sandro R. P. Da Rocha

Pressurized metered dose inhalers (pMDIs) are the preferred inhalation therapy devices, accounting for approximately 80 % of the aerosol drug delivery market. They are also excellent candidates for the delivery of formulations containing biomolecules to and through the lungs. There have been several challenges in the development of pMDI-based formulations since the replacement of CFCs with the more environmentally friendly hydrofluoroalkanes (HFAs). Although the operation of pMDIs with HFAs is similar to those with CFCs, none of the FDA approved surfactants commonly used with CFCs are soluble in HFAs. Therefore, new and highly interfacially active amphiphiles are required for the advancement of HFA-based formulations. Potential surfactant candidates need to be highly soluble in HFAs and also capable of stabilizing dispersed aggregates in the propellant. Within this context, we approach surfactant design by determining surfactant tail solvation and tail-tail interactions at the microscopic level. These interactions are investigated through a combination of *ab initio* calculations and chemical force microscopy (CFM). Binding energies for HFAs and hydrogenated, fluorinated and polar tail chemistries are reported at increasing levels of theory. The results from the *ab initio* calculations are used as a guide to the selection of candidate tails and to provide complementary information to the CFM measurements. Such knowledge is significant not only for the improvement of existing dispersion formulations, where the active component is a hydrophobic drug, but also for the development of novel formulations capable of delivering medically relevant hydrophilic molecules such as peptides, DNA and proteins.

Keywords: hydrofluoroalkanes; inhalers; pMDIs; surfactants; drug delivery; chemical force microscopy; *ab initio* calculations.