Materials chemistry and applications

Modeling halogen bonds in molecular dynamics simulations of active pharmaceutical ingredients

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Many of the active pharmaceutical ingredients (APIs) available on the market today have halogen substituents. These promote non-covalent interactions (e.g., hydrogen and halogen bonds), which can enhance the API properties (e.g., membrane permeability). Hence, a strategy to design new promising APIs is to include halogen atoms within their structure. A cheaper and quicker method to test all the promising APIs during the early stages of drug development is through *in-silico* screenings.[1]

To perform these studies several theoretical methods can be used, such as molecular dynamic (MD) simulations. This methodology relies on molecular force fields that must accurately capture the energetic and structural information of a substance. When applied correctly, this can be used to predict the APIs properties, such as the different solid forms that may arise during the crystallization process of a given molecule (polymorphs). Nevertheless, a prior validation of the force field used needs to be performed. This is based on theoretical predictions of enthalpies of sublimation and unit cell parameters that are compared with experimental results. Structural information can be easily found on the Cambridge Structural Database (CSD) for this validation, however the energetic data that can be correlated to a given crystal phase is rarely found in the literature, particularly for halogenated compounds.[2] In this work, the determination of reference values of enthalpies of sublimation, by Calvet-drop microcalorimetry, for well-characterized single-crystal structures of three halogenated APIs (Figure 1) is described. These results were used to test OPLS-AA based force fields, to determine their ability to accurately describe halogen bonding in solid phases.

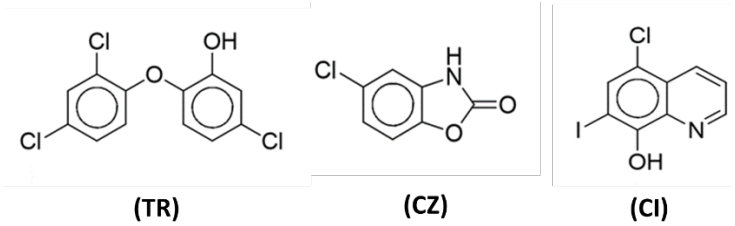

Figure 1: Halogenated APIs investigated in this work: (TR) Triclosan; (CZ) Chlorzoxazone and (CI) Clioquinol.

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