

Thermodynamics of Pharmaceutical Mixtures: From Molecular Modeling to Equation of State Predictions with MAPS

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Abstract

An integrated solution for the calculation of the solubility of pharmaceuticals in various solvents is presented. The proposed strategy is initiated with the calculation of the octanol / water partition coefficient (log P) and the solubility of pharmaceuticals in water (log S). These quantities are calculated by means of descriptors derived from the molecular structure of the pharmaceutical molecules. In Figure 1, the calculated versus experimental values for log P and log S for a set of pharmaceutically relevant compounds are shown. Emphasis was placed on pharmaceuticals with diverse structures, functionality and drugs. Very good agreement was achieved with $r^2 = 0.9$ and $rms = 0.44$. In Figure 2, two selected molecules are presented that reveal the complexity of the structure usually involved in this type of calculations.

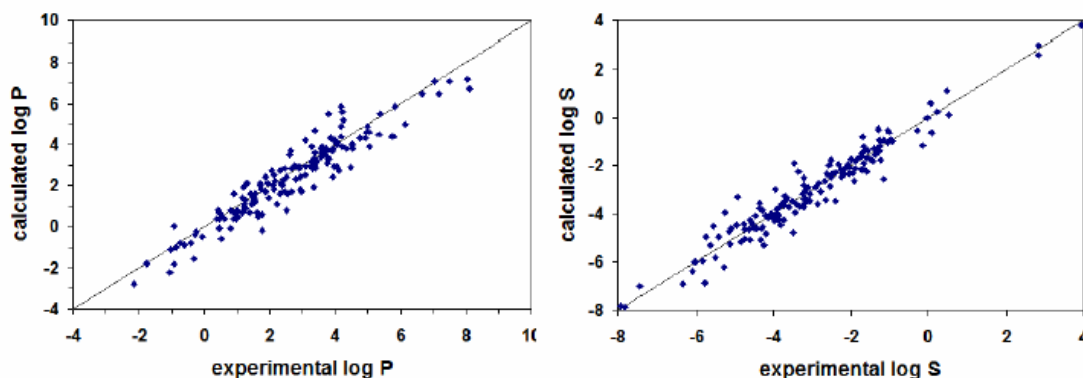


Figure 1. Scatter plot of calculated vs experimental values for log P and log S for 180 drugs and drug-like molecules.

In the second step, the pharmaceutical of interest is modeled with a PC-SAFT-based equation of state via SciTherm (an integrated thermodynamic package in MAPS), using the calculated solubility data at different temperatures. Currently, SciTherm database contains 500 different solvents. Calculations of solubility for pure and mixed solvents are in excellent agreement with experimental data.

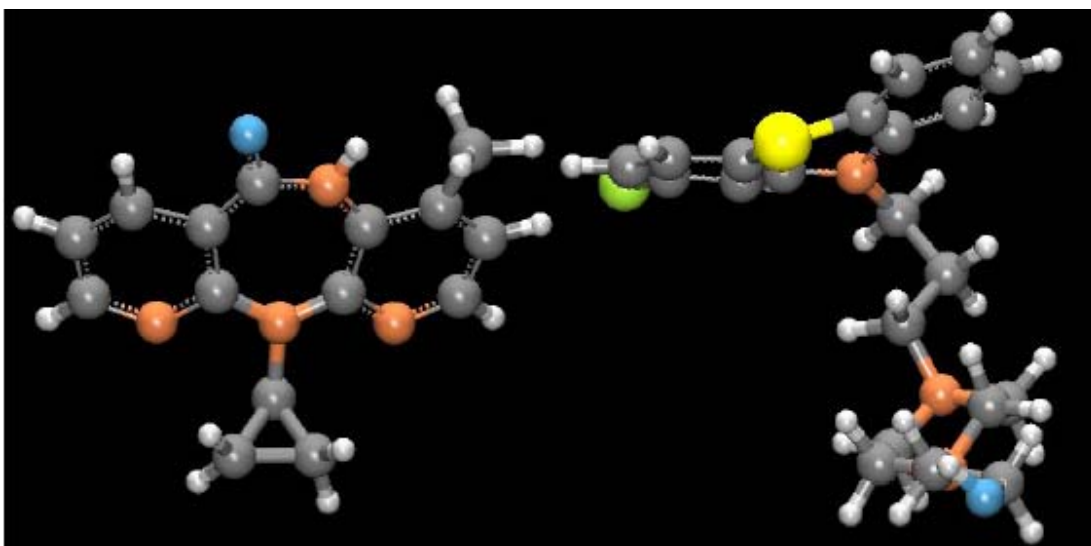


Figure 2: The proposed method is applicable to any pharmaceutical. This is illustrated by the two molecules shown: (left) nevirapine - $C_{15}H_{14}N_4O$ - with log P and log S 2.4 (2.5) and -3.19 (-3.39) (experimental values in parenthesis) respectively and (right) perphenazine - $C_{21}H_{26}ClN_3OS$ - with log P and log S 4.1 (3.9) and -4.13 (-4.16) respectively (experimental values in parenthesis). Color code: Yellow = S; Green = Cl; Orange = N; Blue = O; Gray = C.