

ABSTRACT

Water solubility is an important molecular property for successful development of drugs in pharmaceutical industry. In this work an approximate theory is proposed based on physiochemical properties obtainable from, e.g., conventional Monte Carlo or Molecular Dynamics simulations for the prediction of water solubility of drug compounds. The aqueous solubility is modeled by two subprocesses. One drug molecule is transferred from the pure phase to the vapor phase and from the vapor phase to the aqueous solution. The predicted change in free energy for such a process will then yield the aqueous solubility. For the evaluation of the approximate theory 46-48 drug molecules we have investigated the aqueous phase, the pure amorphous phase at room temperature and at 400 °C, respectively. Results for the change in free energy for the amorphous-vapor process were compared to corresponding results obtained from free energy perturbation simulations combined with thermodynamic integration. Corresponding evaluations are made for the aqueous phases except that in this case only free energy perturbation simulations were carried out. The results presented in this thesis support the use of the suggested approximate theory where the agreement between the predicted and corresponding free energy simulation results are in good agreement for the investigated drug compounds. When the results obtained by the approximate theory are compared to experimental results the agreement is reasonable for a majority of the drug compounds where the ambition is to predict the aqueous solubility to an accuracy of one order of magnitude in $\text{Log}(S_a)$ (amorphous solubility). However, for a few several molecules the deviations from experimental amorphous solubilities are too large. The main reason for these deviations is most likely inaccurate partial charges for certain functional groups such as sulfon, sulfoxide and nitro groups resulting in too strong electrostatic interactions between atoms in the aqueous phase.

ISBN 978-91-628-2277-9