

# Molecular dynamics studies of the formation of pharmaceutical particles by RESS process\*

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## Abstract

With a newly developed method the formation of naphthalene and naproxen particles by *rapid expansion of a supercritical solution* (RESS) is investigated by molecular dynamics (MD) simulations. In this work a new interaction potential model for naproxen is developed.

The new simulation method allows expanding the system very close to the adiabatic curve obtained from reference equations of state, if an adequate expansion velocity is chosen. The expansion paths are also in a good agreement with paths calculated by continuum fluid dynamics simulation for the RESS process. The method shows a good reproducibility and only a small size effect.

The properties of the employed potential models are investigated by simulations of liquid films. With regard to the investigated process the models well reproduce the experimental data, respectively those obtained from equation of state. Simulations of argon films over a range of 1.5 orders of magnitude in system size show that only the pressure of the liquid spinodal is affected significantly by the system size due to capillary waves.

During the expansion the solubility decreases and naphthalene or naproxen particles precipitate. The heat of formation is more than compensated by the Joule-Thomson effect of the expanding solvent CO<sub>2</sub>. Therefore there is no artificial influence of a MD thermostat on the system. Expanding systems from different pre-expansion conditions were analysed according to the nucleation rates and the particle growth. The critical supersaturation is about 10<sup>1.6</sup> up to 10<sup>3.4</sup> and the nucleation rate is in the order of 10<sup>28</sup> cm<sup>-3</sup> s<sup>-1</sup> for both substances.

The classical nucleation theory (CNT) predicts nucleation rates which are many orders of magnitude smaller. The underestimation of the nucleation rate is a typical behaviour of the CNT, and has already been observed for many substances in comparison to experimental and simulation results. Macroscopic models of the RESS process can be improved by rescaling the CNT using the nucleation rates obtained in this work.

The annealed naproxen particles obtained in RESS simulations exhibit another structure than particles which originate from solidification of liquid droplets.

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