Supercritical Fluids as Novel Particle Formation Media: 2. Molecular dynamics simulation of particle formation

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As discussed in the previous article by M. Türk rapid expansion of a supercritical solution (RESS) is a powerful technique for the size reduction of particles. The theoretical treatment of this process can help to understand the detailed steps of the process and to optimize it. In this work here we are investigating the particle formation process by rapid expansion of supercritical solution using molecular dynamics simulations. Molecular dynamics simulation is based on the molecular interactions of the molecules as the only input. It provides insights into the molecular processes of particle and structure formation. A simulation method for the expansion of a solution is developed and applied to solutions of Naphthalene and Naproxen in supercritical carbon dioxide. All properties used in the nucleation theories such as density and surface tension have also been obtained by molecular simulations in order to have a consistent set of data for comparison. The obtained nucleation rates differ depending on the substance by 8 to 20 orders of magnitude to the classical nucleation theory. This is a typical deviation between simulation results and nucleation theory as we know from earlier work, and it is also a typical deviation between experimental data and classical nucleation theory in cases where experimental data are available. Hence, the results obtained in this work can be used to refine nucleation theories to more reliably simulate the complete RESS process.

INTRODUCTION

The formulation process of pharmaceuticals has a significant influence on the properties of the resulting drug with respect to its physical properties. In general one is interested to have fine particles with a larger surface to enhance the solubility and hence the bioavailability. An additional way of solubility enhancement can be the variation of the crystal structure and morphology. A common process is the milling of the material obtained from crystallization. Drugs crystallized from aqueous solutions likely consist of hydrates which may even differ in the amount of included water. This can lead to different structures [1]. Also the shear forces during milling affect the morphology as well as the structure of the substance. This influences the mechanical properties that are relevant for the further processing, for example in the context of tablet processing and tablet porosity [1]. The enhancement of the bioavailability is especially important for drugs having a low solubility in water. Here micronisation processes are required which avoid the problems discussed above and yield very small stable particles with a large surface area.

Rapid expansion of a supercritical solution is such a process suitable for the micronisation of pharmaceutical substances. It yields water free particles in the submicron size, even below 100 nm in advanced variations of the process such as RESSAS which is the expansion into an aqueous solution containing surfactants [2]. The surfactant molecules cover the particle surface avoiding agglomeration and hence maintaining the original particle size and structure. Experimentally it is very difficult to investigate the particle formation process itself since the

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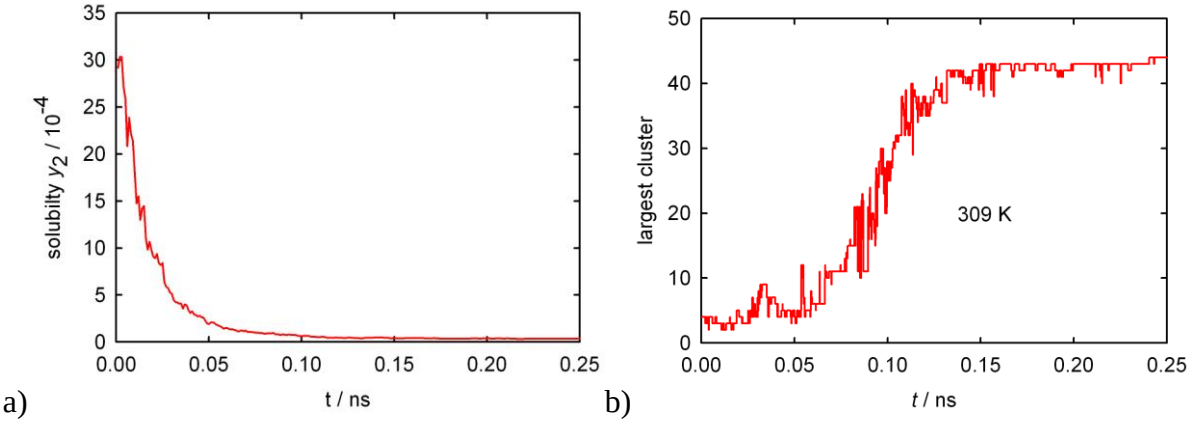
critical cluster size is very small. For engineering modeling of the complete RESS process the nucleation rate is required which has to be estimated by models such as the classical nucleation theory. It is known that these models are not accurate and may differ over many orders of magnitude from experimental data. In this context molecular dynamics simulation of the particle formation within RESS and RESSAS provides a detailed insight into the molecular processes. This includes the initial steps of the formation of structure and morphology of particles which are not accessible experimentally. Furthermore, properties of the particles itself and the nucleation and growth process that are required for the modeling of the complete process are provided.

METHOD

Molecular dynamics (MD) simulation is employed for the investigation of the particle formation with RESS. In MD simulations the Newton's equations of motion are solved for each atom in the force field of all other atoms numerically. Energy conservation requires a time step in the order of 10^{-15} s, hence for the simulation of one nanosecond 10^{6} steps are necessary. The only input of this simulation method is a model for the interaction between the atoms and molecules. Based on such model one can calculate macroscopic properties from the microscopic interactions.

For the purpose of the simulation of RESS we have developed a simulation method mimicking the adiabatic expansion of a fluid [3]. The supercritical solution at given high pressure and high temperature is equilibrated for about one nanosecond. The concentration of the solute is close to the solubility limit in order to avoid the formation of clusters already in the initial supercritical solution. A possible cluster formation is monitored by the calculation of the largest cluster in the system. If its value remains in the order of one or two molecules the solution is stable. The equilibrated supercritical solution is then expanded by increasing the size of the simulation box in all three dimensions in many small steps. A thorough investigation has shown [3] that 100 expansion steps is a good choice to be accurate enough and to minimize the computational effort. At each expansion step the system is simulated in a constant energy ensemble (NVE) for a period of typically 2.5 ps.

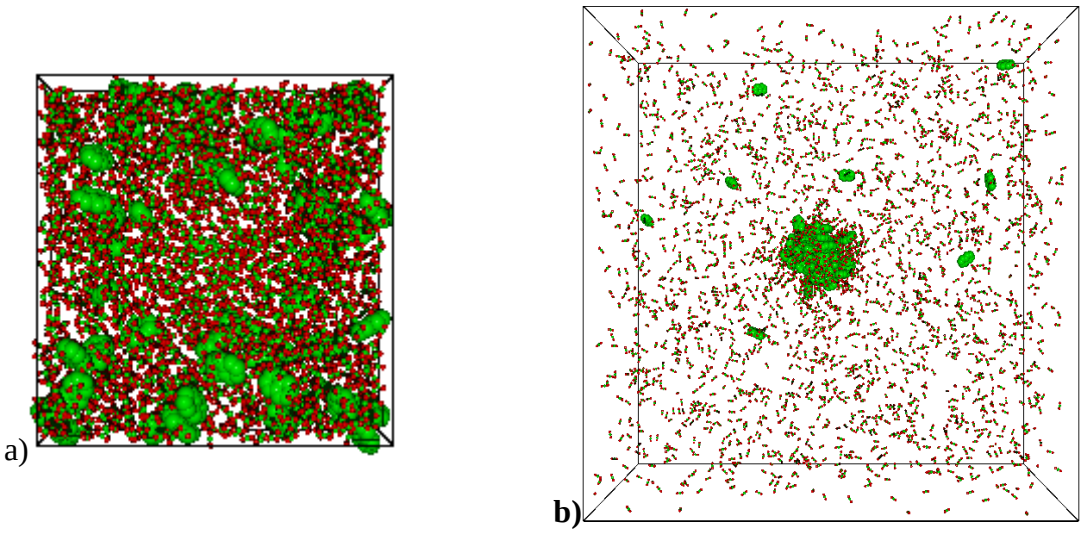
From the configurations obtained by the MD simulations we calculate the thermodynamic properties such as pressure and temperature as well as the cluster size distribution. From the cluster size distribution one can calculate the nucleation rate by the method of Yasuoka and Matsumoto [4]. The supersaturation is obtained form the solubility calculated with a correlation model for Naphthalene [5] and Naproxen [6,7] representing the experimental solubility limit. It is evaluated at each expansion step for the temperature and pressure given at that step. Since pressure as well as temperature decrease during the expansion also the solubility does. In Figure 1a an example for the solubility of Naphthalene in supercritical CO_2 during an expansion simulation is shown. One can see that it rapidly reaches a very low value corresponding to a very high supersaturation of Naphthalene in the homogenous solution. The size of the largest cluster is employed as an indicator of the growth here as shown in Figure 1b. At about 0.05 ns the solubility is already quite low and the system starts to form clusters. The cluster formation removes molecules form the solution which then decreases the supersaturation. As the relevant supersaturation for the particle formation we calculate the average of the supersaturation in the period of time in which the nucleation takes place. This period of time can be determined from the cluster size statistics as plotted according to the method of Yasuoka and Matsumoto [4].



a) b)

Figure 1 : a) Solubility of Naphthalene in CO_2 during the expansion simulation as function of time. b) Size of the largest cluster as function of time corresponding to a).

To illustrate the expansion simulation two snapshots of the simulation box are shown in Figure 2. Figure 2a is a snapshot of the equilibrated supercritical solution before the expansion. The CO_2 molecules are depicted smaller in order to have a view into the dense solution. After the expansion the system consists of one cluster surrounded by the CO_2 gas phase with few Naphthalene molecules (Figure 2b). The remaining Naphthalene molecules in the gas phase are due to relatively high vapour pressure of naphthalene. It should be mentioned that actual difference in size between the simulation boxes is much larger than shown in Figure 2.



a) **b)**

Figure 2 : Snapshots of the simulation box before the expansion a) and after the expansion b). The size of the CO_2 molecules is reduced for better visibility. The size difference of the boxes is actually much larger than shown here.

RESULTS

In order to verify the expansion simulation we have first compared the data obtained from an expansion of pure CO_2 to that of equation of state calculations for an adiabatic expansion. Here we choose a reference equation [8] which accurately represents the experimental data of CO_2. One can see in Figure 3b that the simulation data for the CO_2 expansion and the adiabatic curve obtained from the equation of state agree very well. Hence the simulation method represents the adiabatic expansion of a supercritical system.

In the next step, a solution of Naphthalene in supercritical CO_2 with the mole fraction x_{naphta}=0.02572 is expanded in the same way. The expansion path in the pressure-temperature diagram is shown in Figure 3b. It is close, basically parallel to the expansion curve of pure CO_2. The progression of the temperature with the expansion time is compared in Figure 3a. The temperature decreases slower for the Naphthalene solution than for the pure solvent which in part is related to the formation of particles and the latent heat of condensation associated with it. The expansion of a Naproxen leads to an even slower temperature drop because the additional coulomb interaction leads to larger latent heat. This is the case although the mole fraction of Naproxen is much smaller namely x_{naprox}=0.00826. If one chooses the same mole fraction for Naphthalene it leads to a significant temperature rise at the end of the expansion when the particles form. However, such Naproxen concentration is significantly above the solubility limit and hence not used here. In the pressure-temperature projection the expansion path of the Naproxen solution is also very close to that of pure CO_2 as shown in Figure 3b.

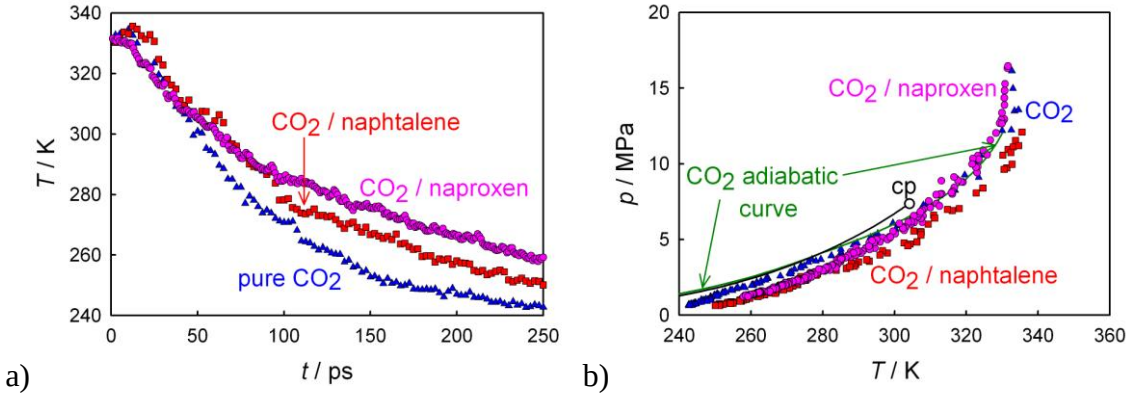


Figure 3 : Expansion path: a) temperature as function of the simulation time. b) Pressure plotted versus the corresponding temperature during the expansion. Triangles: pure CO_2; circles: Naproxen in CO_2; squares: Naphthalene in CO_2; cp: critical point of pure CO_2.

An important property of the particle formation process is the nucleation rate. There are up to day no experimental data for the nucleation rates of the RESS process available, probably due to the difficulties in the detection of very small particles in an expanding supercritical solvent. Modelling of the RESS process relies on the capability of nucleation theories to predict nucleation rates from properties of the macroscopic phase of the nucleating substance. The only access to nucleation rates for RESS is the continuum fluid dynamics modelling using a nucleation theory model as described in the preceding paper. By comparison of the measurable properties such as particle size distribution one can obtain the nucleation rate as by-product. Its accuracy depends on the accuracy of the employed nucleation theory. For large organic molecules including pharmaceutical substances it is even difficult to get the

properties required for nucleation theories such as surface tension or the density. With the molecular simulation method developed here one can calculate the nucleation rate directly from the molecular interactions. During the simulation all configurations are stored on a hard disk for subsequent analysis. With the above mentioned method of Yasuoka and Matsumoto one can calculate the nucleation rate from the cluster size statistics obtained from the analysis of the stored configurations. In Figure 4 some representative values are plotted for Naphthalene and Naproxen for three different temperatures each. The estimations by the classical nucleation theory of Becker and Döring [9] are added as curves for the corresponding temperature. The properties used in the theory are obtained by simulation from the same interaction model as used in the nucleation simulation. So if the theory is correct the curves should go right through the points. This is obviously not the case. All curves are significantly below the simulation data by about 10 orders of magnitude in case of Naphthalene and 20 orders of magnitude in case of Naproxen. It should be mentioned that due to its nature deviations and uncertainties of nucleation rates are in the order of magnitudes rather then percent, nevertheless the deviations found here are very large. They show that classical nucleation theory is not a reliable model to estimate nucleation rates. This applies not only to the Becker-Döring [9] version but also to others such as the Girshick-Chou version [10]. The estimations by these type of nucleation theories is somewhat different but still in big distance to the simulation data.

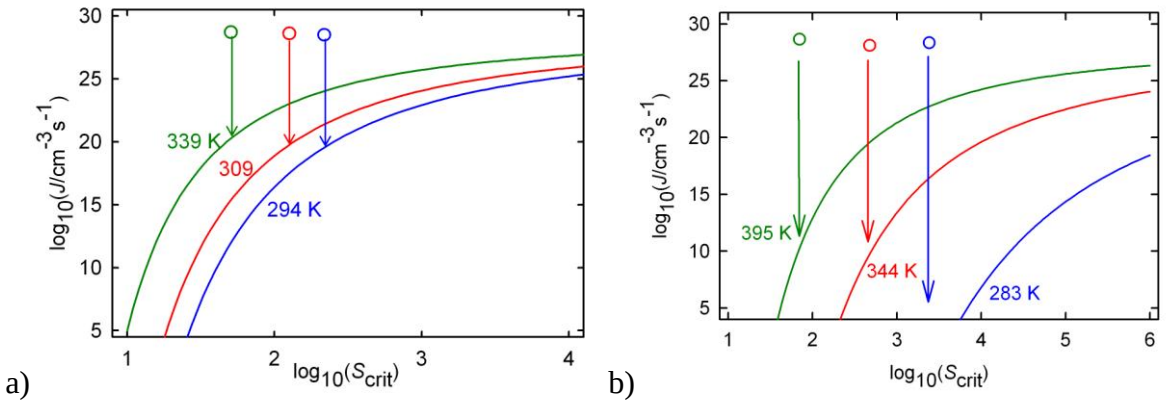


Figure 4 : Nucleation rates; a) Naphthalene. b) Naproxen. Circles: MD results; curves: estimations with the classical nucleation theory.

CONCLUSION

One may ask the question why one should thrust molecular simulation data more than nucleation theories since both are theoretical methods and experimental data for comparison are not available. In molecular simulation a model for the molecular interaction is used as input representing the properties of a substance. In principle such model is valid for all properties; however, it is known that some potential models are more accurate for some properties than for other. Still one can use a reliably developed potential model for the extrapolation of properties for that no experimental data are available. In case of the substances investigated here we have tested the model with respect to several properties for which experimental data are available for comparisons. These are the density, the surface tension, as well as the self diffusion coefficient. Since the models accurately represent these

properties we can expect that other properties related to these, such as nucleation rates, are also represented in reasonable accuracy. Furthermore, we know from several investigations of other substances such as argon or zinc [11] that the molecular dynamics simulation of nucleation gives nucleation rate values also significantly above the prediction by the classical nucleation theory. There are several problems with the classical nucleation theory and many of its further developments. First of all, the properties required for the evaluation of the classical nucleation theory are those of macroscopic systems while the critical cluster are in the order of few molecules at given supersaturation. In addition by far most nucleation theories assume an isothermal nucleation process which is clearly not the case. Further assumptions of the classical nucleation theory such a as an ideal gas phase are not given in the RESS process having compressed gases.

A consequence of this investigation is that one can improve the modelling and the optimization of a RESS process relying on models for the nucleation rate by rescaling the curves obtained from classical nucleation theory. This rescaling is somewhat similar to the approach of experimentalist to rescale nucleation theories in order to be consistent with experimental data [12]. Considering the large deviation between the classical nucleation theory and the simulation data points one might expect a significant quantitative effect of the results of the RESS modelling.

Furthermore, we find that especially in case of hydrogen bonding substances such as Naproxen the local ordering of the molecules is different for the RESS process and the crystallisation from the liquid phase. This likely affects also the further growth of the particles by attachment of further molecules.

We here find agreement with the expansion path obtained by continuum fluid dynamics simulation in the preceding paper of M. Türk and by molecular dynamics simulation here. This is although we do not consider fluid flow dynamics in the MD simulations. The reason is that the expansion simulated by MD is always before the Mach disc.

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