Estimation of melting point depression driven by CO_2 from molecular informatic approach

Yuna Tatsumi , Yasuhiko Orita, Hung Ying Chieh, and Yusuke Shimoyama

Department of Chemical Science and Engineering, Tokyo Institute of Technology, Japan
S1-33 2-12-1 Ookayama, Meguro-ku, Tokyo 152-8550 Japan

Background In order to improve solubility and dissolution rate of pharmaceutical products, formation of pharmaceutical composites composed of active pharmaceutical ingredients (APIs) and additives are focused on so far. A hot melt extrusion, which is one of the methods to produce pharmaceutical composites, is considered as the potential production method [1]. However, a thermal decomposition of the APIs in this process can occur because of the heating process to melt additives. In this study, we focus on melting point depression driven by CO_2 for lipids. By using this melting point depression, the pharmaceutical composite can be formed at the lower temperatures. Knowledge of lipid melting point depression driven by CO2 is useful and important for process design of the pharmaceutical composite fabrication. We propose a estimation method of melting point depression driven by CO_2 from molecular informatic approach.

Calculation Melting point depression by CO_2 can given from solid-liquid-gas equilibrium criteria using the following equations:

$$f_1^V = f_1^L, f_2^V = f_2^L = f_2^S \quad (1)$$

where *f* is the fugacity, each subscript is 1 for CO_2 and 2 for solid solute, and superscripts S, L, and V mean solid, liquid, and vapor phases. In order to calculate the fugacity of liquid and vapor phases, Peng-Robinson equation of state (PR-EOS) is used because of high pressure conditions on the solid-liquid-gas phase equilibrium calculation. PR-EOS is given as follows:

$$p = \frac{RT}{v-b} - \frac{a}{v(v+b)+b(v-b)} \quad (2)$$

where a is molecular interaction parameter and b is molecular volume parameter. These parameters for mixtures are calculated by the van der Waals type mixing with binary interaction parameter fitted to the experimental data. In this work, molecular informatic approach is proposed for estimation of melting point depression driven by CO_2 as shown in Figure 1. Molecular information, such as molecular surface area and surface charge density from a quantum calculation is used for determination of PR-EOS parameters.

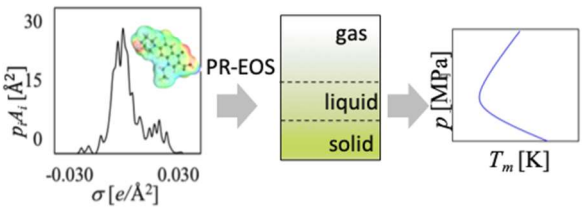

Figure 1. A model for estimating the melting point depression from molecular information

Result and Discussion Figure 2 shows the results of the melting point depression driven by CO_2 estimated from molecular informatic approach in this work. As given in Figure 2., the estimated melting point curves for benzoic acid and naphthalene represents the experimental data well. It's confirmed that this molecular informatic approach can give good estimation for 13 solid solutes. We conclude that this estimation method can be useful for the pharmaceutical composites using melting point depression driven by CO_2.

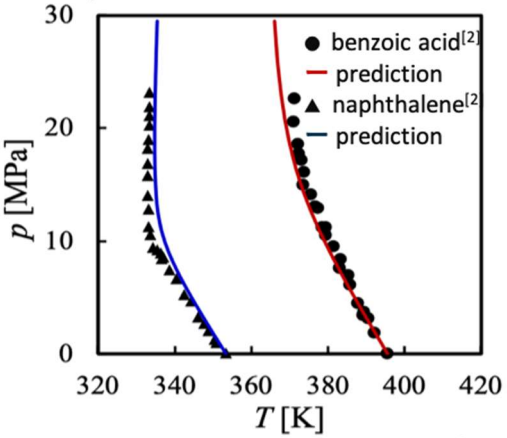

Figure 2. Comparison of experimental and predicted melting point

[1] M. Gajda *et al.*, Int. J. Pharm., **569**, 118579, 2019.
[2]E. Bertakis *et al.*, J. Supercrit. Fluids., **41**, 238-245, 2007