APPLICATION**NOTE**

Melting Point Effect of High Pressures of CO_2 on a Pharmaceutical Compound Demonstrated with HP-DSC

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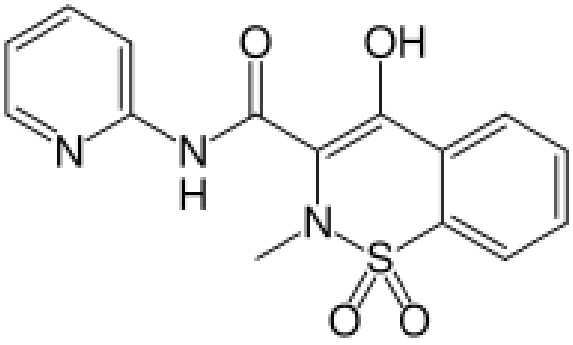
Introduction

The melting temperatures of various solids such as certain polymers, fatty acids, ionic liquids, and pharmaceutical compounds have been found to be lowered substantially in the presence of supercritical carbon dioxide ($scCO_2$) due to the solubility of the CO_2 in the melt. This effect can be beneficial for processing or crystallizing the materials from their melts, especially if they are thermally sensitive. The susceptibility of a material to melting point depression in the presence of $scCO_2$ can be explored by using high pressure DSC (HP-DSC) to measure the melting temperature of the material under elevated pressures of CO_2, even without reaching supercritical conditions. In this study, the effect of high pressures of carbon dioxide on the melting point of the pharmaceutical compound piroxicam, a non-steroidal anti-inflammatory drug (NSAID), was investigated. Four anhydrous crystalline forms (polymorphs) of this compound have been reported [1]. Commercially available form I, with a melting temperature of ca. 201°C, is the most stable crystalline form. The melting point of form I has been shown to be depressed substantially in the presence of $scCO_2$ [1]. Since piroxicam decomposes upon melting, lowering the melting point of the compound could be beneficial for growing other crystalline forms (e.g., form III) from the melt that are difficult to access by crystallization from solutions in organic solvents.



Piroxicam

Experimental Details

Piroxicam (TCI America) was used as received. DSC measurements were performed with the NETZSCH DSC 204 HP *Phoenix*® on 4-6 mg samples in open 25 µL aluminum crucibles. Samples were heated at 10 K/min under a flow of N_2 or CO_2 with pressures ranging from 1 to 40 bar at a flow rate of 100 mL/min or under a static CO_2 atmosphere for achieving pressures of >55 bar. An indium standard was used to verify the temperature calibration of the instrument, which did not vary under the different atmospheres and pressures.

Results

Figure 1 shows the melting transitions in the DSC curves of piroxicam form I under ambient CO_2 pressure and CO_2 pressures of 40 bar and 63 bar. Whereas measurements at ambient pressure and 40 bar were performed under a dynamic flow of CO_2, the measurement at

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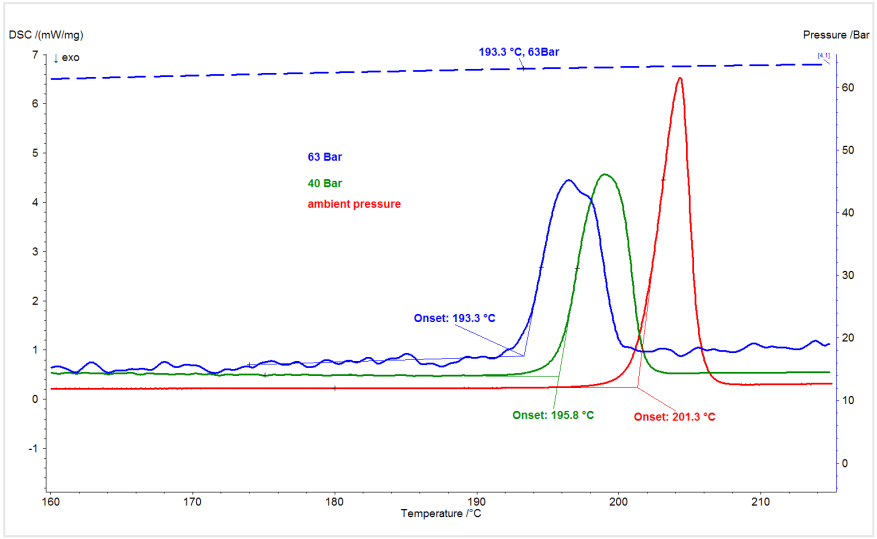
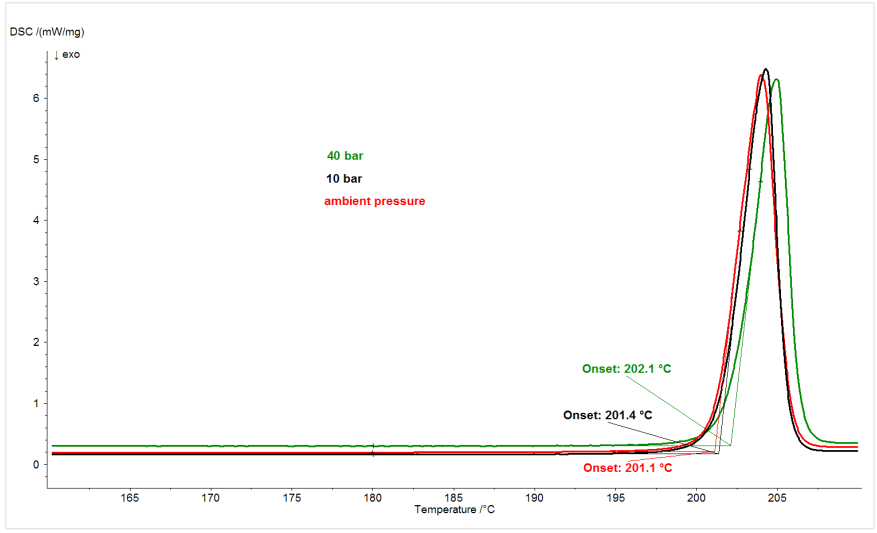
63 bar was performed under a static atmosphere of CO_2 in a closed system. The maximum pressure of 55 bar from the CO_2 tank was admitted to the HP-DSC at ambient temperature, and the system was closed so that the pressure increased with heating, reaching 63 bar at the onset of sample melting. The extrapolated onset temperature of the piroxicam melting peak of 201.3°C at ambient pressure is consistent with the literature value[1]. The melting onset was depressed by approximately 5.5 K to 196°C under 40 bar CO_2. It decreased by an additional 2.5 K under a CO_2 pressure of 63 bar.



1 DSC thermogram of piroxicam form I (10 K/min) under CO_2

To verify that the melting point depression effect on piroxicam by increasing CO_2 pressure was specific to CO_2, the effect of increasing N_2 pressure on the melting behavior of the compound was examined. Figure 2 shows the melting peaks of piroxicam under N_2 at ambient pressure, 10 bar, and 40 bar. In contrast to the melting point depression effect of increasing CO_2 pressure, increasing N_2 pressure caused a slight increase in the melting point of piroxicam, consistent with the behavior of most materials, which undergo expansion when changing from solids to liquids.



2 DSC thermogram of piroxicam form I (10 K/min) under N_2

Summary

HP-DSC measurements showed that piroxicam undergoes a melting point depression of approximately 8 K in the presence of a CO_2 atmosphere of 63 bar compared to the situation at ambient pressure. This study demonstrated the utility of HP-DSC measurements for screening solids for potential melting point depression in $scCO_2$, even when the pressures are below what is necessary to reach the supercritical phase.

Literature

[1] F. Vrečer, M. Vrbinc, and A. Meden, "Characterization of Piroxicam Crystal Modifications", Int. J. Pharmaceutics, Vol. 256, pp. 3–15, 2003.

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