The effect of pressure on the melting point of Pluronics® in pressurised carbon dioxide

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Abstract-
The melting points of Pluronic® F-77, F-127, F-68, F-38 and F-108 were investigated in pressurised CO₂ between a pressure range of (2.0 to 50.0) MPa. Unprocessed and CO₂-processed Pluronic® samples were analysed by differential scanning calorimetry (DSC) and powder X-ray diffraction (PXRD). A melting point depression in the range of (18.1± 0.5 to 19.3± 0.3) K was observed for all Pluronics® studied in this work. The melting point of Pluronics® in pressurised CO₂ was found to be independent of their molecular weight and poly (propylene oxide) [PPO] content. Analysis by DSC and PXRD revealed that CO₂ processing had no impact on the morphology of Pluronics®.

Introduction-
Any substance above its critical temperature and pressure can be defined as a supercritical fluid 1. A supercritical fluid has liquid-like density and gas-like diffusivity which can also be tuned by varying operational temperature and pressure 2. SCCO₂ is by far the most commonly used supercritical fluid because of its low critical temperature (304.3 K) and critical pressure (7.33 MPa). Moreover, it is readily available, nontoxic, non-flammable, non-corrosive, inexpensive, environmentally benign and easy to remove from reaction systems. SCCO₂ has found its use in the chemical industry as an alternative to organic solvents and it is also considered to be desirable for the processing of thermolabile materials 3,4. Supercritical fluid technology has applications in a variety of fields such as, extraction, cleaning, synthesis etc. 5. One such application includes polymer processing. The interaction of CO₂ with polymers is an interesting phenomenon and plays a significant role in various polymer processing operations 6-8.

The depression in melting point (T_m) or glass transition (T_g) temperature in polymers due to the sorption of CO₂ is a well-known phenomenon which is dependent on various factors such as crystallinity and presence of CO₂-philic moieties 9-14. Amorphous polymers are reported to show higher interactions with CO₂ than crystalline polymers 15,16. These interactions can be
enhanced by the incorporation of functionalities e.g. ether linkages, carbonyl and fluro groups \(^8,16-19\). The reduction in \(T_m\) or \(T_g\) is a colligative property which is simply not a hydrostatic pressure effect but depends upon the \(CO_2\)-polymer interactions \(^8\). This phenomenon provides an exciting opportunity for the processing of polymers at low temperatures in operations such as coating, impregnation and particle engineering.

Pluronics® or poloxomers (non-proprietary name) are block copolymers consisting of hydrophilic poly (ethylene oxide) [PEO] and hydrophobic poly (propylene oxide) [PPO] segments arranged in a PEO-PPO-PEO tri block structure (A-B-A). The structure of a pluronic block copolymer is presented in Figure 1.

![Figure 1: Generalized structure of a pluronic molecule; where x and y are positive integers](image)

Pluronics® are synthesised by sequential polymerisation; where, the PPO block is synthesized followed by growth of PEO chains at both ends of PPO block. This reaction is generally carried out in the presence of an alkaline catalyst such as sodium hydroxide which is then neutralised and removed \(^20\). Pluronics® are semi-crystalline in nature where, PEO units impart crystallinity to the polymer \(^21,22\). The physical properties of Pluronics® are dependent upon their molecular weight and PPO-PEO ratios. Pluronics® studied in this work are all solids at room temperature and other properties such as molecular weight, melting point and PPO-PEO ratios are presented in Table 1. The polydispersity index of F-68 and F-127 has been reported in literature as 1.4 \(^23\).

<table>
<thead>
<tr>
<th>Pluronic</th>
<th>Average Molecular weight (^24) (g/mol)</th>
<th>Melting point ((K))</th>
<th>Average Weight (EO)</th>
<th>Average Weight (PO)</th>
<th>Average (2x)</th>
<th>Average (Y)</th>
<th>Average EO:PO units</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-38</td>
<td>4600</td>
<td>321.15</td>
<td>3680</td>
<td>920</td>
<td>84</td>
<td>16</td>
<td>5.3 : 1.0</td>
</tr>
<tr>
<td>F-68</td>
<td>8400</td>
<td>325.15</td>
<td>6720</td>
<td>1680</td>
<td>152</td>
<td>29</td>
<td>5.2 : 1.0</td>
</tr>
<tr>
<td>F-108</td>
<td>14600</td>
<td>330.15</td>
<td>11680</td>
<td>2920</td>
<td>266</td>
<td>50</td>
<td>5.3 : 1.0</td>
</tr>
<tr>
<td>F-77</td>
<td>6600</td>
<td>321.15</td>
<td>4620</td>
<td>1980</td>
<td>106</td>
<td>34</td>
<td>3.1 : 1.0</td>
</tr>
<tr>
<td>F-127</td>
<td>12600</td>
<td>329.15</td>
<td>8820</td>
<td>3780</td>
<td>202</td>
<td>65</td>
<td>3.1 : 1.0</td>
</tr>
</tbody>
</table>
Table 1: Physical properties of Pluronics®

Pluronics® are generally regarded as safe (GRAS) and listed in the US and British Pharmacopoeia. They are widely used excipients as antifoaming agents, wetting agents, dispersants, thickeners and emulsifiers. Pluronics® interact with hydrophobic surfaces and biological membranes due to their amphiphilic nature and have been shown to modify the biological response by overcoming drug resistance in cancer and promoting drug transport across cellular barriers.

The solubility of low molecular weight Pluronics® in CO₂ has been discussed in the literature but information on its interaction with higher molecular weight Pluronics® is uncommon. The aim of this work was to study the effect of PPO-PEO ratio, molecular weight and pressure on the melting behaviour of higher molecular weight Pluronics® in CO₂.

MATERIALS AND METHODS

Materials- The reagents used in this study (listed in Table 2) were used without further purification. Liquid carbon dioxide was obtained from BOC Ltd with a purity of 99.9%.

<table>
<thead>
<tr>
<th>Pluronics</th>
<th>Source</th>
<th>Batch number</th>
<th>Viscosity (cps at 77 °C)</th>
<th>Specific gravity (77°C/25°C)</th>
</tr>
</thead>
<tbody>
<tr>
<td>F-127</td>
<td>Sigma</td>
<td>086K0026</td>
<td>3100</td>
<td>1.05</td>
</tr>
<tr>
<td>F-77</td>
<td>BASF</td>
<td>WPDA559B</td>
<td>480</td>
<td>1.04</td>
</tr>
<tr>
<td>F-38</td>
<td>BASF</td>
<td>WPMB554B</td>
<td>260</td>
<td>1.07</td>
</tr>
<tr>
<td>F-68</td>
<td>Sigma</td>
<td>BCBD6489V</td>
<td>1000</td>
<td>1.06</td>
</tr>
<tr>
<td>F-108</td>
<td>Fluka</td>
<td>0001375698</td>
<td>2800</td>
<td>1.06</td>
</tr>
</tbody>
</table>

Table 2: Description of materials used

Determination of melting temperature of Pluronics® in CO₂ at various pressure values

The melting point depression at pressure ranging from 2.0 to 50.0 MPa was determined using a phase monitor (Supercritical Fluid Technologies (SFT) Inc.). A schematic diagram of the phase monitor is shown in Figure 2. The phase monitor has a manually controlled syringe.
pump attached to a 30 ml pressure vessel. A CCD camera with a fibre optic light source is attached to the vessel and allows clear viewing of the vessel’s interior. The pressure vessel also contains an internal magnetic stirrer for effective mixing. Heating of the vessel is controlled by an internal resistance thermometer up to a maximum temperature of 150 °C. Solid or liquid samples are placed in a glass capillary tube which is held securely on the sample holder at the optimal viewing position.

![Schematic diagram of supercritical phase monitor](image)

Figure 2: Schematic diagram of supercritical phase monitor

Instrument was calibrated using naphthalene as standard prior to the experiments. The melting point capillary was filled with approximately (1-3) mg of sample and placed in the sample holder which is then tightly screwed on to the pressure vessel. CO₂ was introduced into the vessel to achieve the desired pressure; which was then kept constant during the experiment by manually rotating the piston. The temperature was increased in increments of 0.2 K until the complete melt was observed. The melting of Pluronics® was monitored through a quartz window via a camera attached to the vessel. Figure 3 presents an example of Pluronic F-68 at various stages of the experiment. The data discussed in this work was collected at point d (Figure 3) for all pluronics. The experiments were conducted at various
pressures (i.e. 2.0, 4.0, 6.0, 8.0, 10.0, 15.0, 20.0, 30.0, 40.0 and 50.0 MPa) and the results were recorded in triplicate.

Figure 3: Various stages of the experiment. [Pluronics F-68 at the; (a) Beginning of the experiment, (b) After the introduction of CO\textsubscript{2}, (c) Start of melting (d) Complete melt]

**Powder X-ray Diffraction**- The diffractograms of the processed and unprocessed samples were obtained using a D8 Advanced diffractometer (Bruker). Samples were analysed at room temperature and in transmission mode using Mylar film for support. The samples were rotated at 15 rpm and data was collected between 2.5 to 50° 2\theta, at a scan rate of 0.2°/s using Cu Kα radiation.

**Differential Scanning Calorimetry**- The thermograms of processed and unprocessed Pluronics® were recorded using DSC-1 calorimeter (Mettler Toledo). Samples (5-8 mg) were weighed in standard aluminium pans and thermograms were recorded from 298.15 K to 378.15 K at heating rate of 10 K/ 60 s.

**RESULTS AND DISCUSSION**

The melting points of Pluronics® at atmospheric pressure were determined using DSC and compared with their respective melting points in CO\textsubscript{2}. Table 3 shows the melting temperature of Pluronics® at atmospheric pressure (0.1 MPa) and at different pressure values in CO\textsubscript{2}.
<table>
<thead>
<tr>
<th>Pressure (MPa)</th>
<th>Melting point mean (K) ± Standard deviation (n=3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>F-77</td>
</tr>
<tr>
<td>0.1*</td>
<td>319.6</td>
</tr>
<tr>
<td>2.0</td>
<td>317.9 ±0.2</td>
</tr>
<tr>
<td>4.0</td>
<td>312.9 ±0.3</td>
</tr>
<tr>
<td>6.0</td>
<td>307.1 ±0.3</td>
</tr>
<tr>
<td>8.0</td>
<td>301.3 ±0.6</td>
</tr>
<tr>
<td>10.0</td>
<td>302.1 ±0.3</td>
</tr>
<tr>
<td>15.0</td>
<td>301.7 ±0.4</td>
</tr>
<tr>
<td>20.0</td>
<td>300.4 ±0.2</td>
</tr>
<tr>
<td>30.0</td>
<td>300.3 ±0.2</td>
</tr>
<tr>
<td>40.0</td>
<td>300.6 ±0.2</td>
</tr>
<tr>
<td>50.0</td>
<td>301.1 ±0.2</td>
</tr>
</tbody>
</table>

Table 3: Melting point of Pluronics® in CO\textsubscript{2} at different pressure values (* values determined by DSC)

The Pluronics® in CO\textsubscript{2} were found to melt at \((18.1 ± 0.5 \text{ to } 19.3 ± 0.3)\) K below their actual melting point. The melting point depression data presented in Figure 4 show two distinct regions where melting point decreases almost linearly with the pressure increase in the “region A”, followed by “region B” with no further changes. A similar melting point depression trend has been reported for polycaprolactone and poly(butylene succinate) in the pressure range of 0.1 to 27.6 MPa and 0.1 to 20.7, respectively\textsuperscript{31}. On the other hand, compounds such as fatty acids, octacosane and naphthalene show an initial decrease followed by an increase in the melting point with the increase in pressure\textsuperscript{12,32}. The initial decrease in melting point is attributed to the solubility effect and the increase in melting point at higher pressures is due to the pressure effect. This is mainly because CO\textsubscript{2} at low pressures acts as a plasticising solvent which reduces the melting point of Pluronics®; whereas, the application of higher pressures increases the melting point\textsuperscript{7,33}. Similarly, recent studies have shown that ionic salts also demonstrate melting point depression in CO\textsubscript{2}. Their melting behaviour was comparable to Pluronics® in the pressure range of 0.1 to 40 MPa\textsuperscript{34,35}. 
The melting point depression is widely accepted to occur due to the increase in polymer free volume and segment mobility caused by the dissolution of CO₂ in the matrix. The degree of depression is dependent on CO₂'s ability to interact with CO₂-philic functional groups present in an excipient. Studies have shown that CO₂-polymer mixing is favoured by the presence of carbonyl groups in polymers by Lewis acid-base interactions. Similarly, the presence of ether linkages in polymers has also shown to aid the CO₂-polymer interactions, which depend upon the accessibility of ether oxygen. For example, it has been reported that PPO is relatively more CO₂-phillic than PEO. This is thought to be due to the weaker intermolecular forces in PPO because of an extra methyl group per monomer unit. This explains the solubility behaviour of small and medium molecular weight Pluronics® in CO₂ where increases in overall molecular weight and PEO content decrease its solubility. The solubility of lower molecular weight (up to 3738 g/mol) Pluronics® decreases with the decrease in PPO/PEO ratio for a given molecular weight. Conversely, solubility of Pluronics® in CO₂ increases with the increase in molecular weight for a particular PPO/PEO ratio.
Figure 5: Comparison of melting point depression of Pluronics® with molecular weight where, ($\Delta T = T_m$ measured by DSC – $T_m$ at 30 MPa).

Figure 6: Comparison of melting point depression of Pluronics® with PPO units where, ($\Delta T = T_m$ measured by DSC – $T_m$ at 30 MPa).
Hence, it was expected that Pluronics® studied here with higher CO₂-philic PPO content will show larger melting point depressions. However, Figure 5 and 6 suggest that the interaction of CO₂ with Pluronics® was independent of PPO content and molecular weight. This can be explained by the cohesive energy density of the polymers. It has been reported that, as the number of favourable CO₂-polymer interactions increases, the enthalpy of mixing may become more favourable whereas the entropy of mixing decreases. Increasing the number of CO₂ interacting monomer units may also decrease the entropy of mixing by hindering the segmental motion. This increase in monomer units is believed to enhance the cohesive energy density of the copolymer only to an extent after which it may no longer favour the enthalpy of mixing. Therefore, as the Pluronics® used in this study have large numbers of CO₂-polymer interacting groups (ether linkages) corresponding to high cohesive energy density such that the enthalpy of mixing is not favoured. This explains the similar melting point depression for all studied Pluronics®.

It is also important to note that the interaction of CO₂ with polymers is a complex phenomenon which depends upon numerous factors like number and ease of accessibility of CO₂-philic functionalities, polymer molecular weight, intermolecular bonding, structural regularity, chain flexibility, copolymerization etc. Therefore, more extensive studies similar to this work at even higher pressure values are required to deduce the phase behaviour of Pluronics® in CO₂.

**Differential scanning calorimetric analysis**

DSC analysis was performed on CO₂ processed and unprocessed Pluronics®. The thermograms presented in Figure 7 showed similar onset of melting/melting peaks for all Pluronics®. Any appearance of a shoulder in the peaks was due to the presence of admixtures of propylene oxide homopolymer with di or tri block copolymers. Any difference in the peak height was due to the sample size. This indicates that CO₂ processing had no effect on thermal properties of Pluronics®.
Figure 7: Thermograms of SCCO$_2$ processed and unprocessed Pluronics®

**Powder X-ray diffraction analysis**

PXRD analysis was performed on the processed and unprocessed samples of Pluronics® to identify occurrence of any morphological changes due to CO$_2$ processing. Peaks at 20 values of 19 and 23° (Figure 8) were present for all Pluronics® and diffractograms of processed and unprocessed samples were identical. This confirms that the CO$_2$ processing did not cause any changes to the crystal structure of studied excipients. Pluronics® are semi-crystalline in nature due to crystalline structure of PEO fraction and the peaks observed match with the published standard PXRD pattern of PEO (International Centre for Diffraction Data ICDD, file number 49-2201). PPO fraction in the Pluronics® is present in amorphous form.$^{21}$
Conclusions

In this study, it was observed that pluronic F-77, F-127, F-38, F-68 and F-108 melted at (18.1± 0.5 to 19.3± 0.3) K below their actual melting point in CO$_2$. This melting behaviour of Pluronics® in CO$_2$ was found to be independent of their molecular weight and PPO content. DSC and PXRD analysis of processed and unprocessed samples of all Pluronics® indicated that CO$_2$ processing has no impact on their crystal morphology. The current study provides a better understanding of melting behaviour of Pluronics® in CO$_2$ at pressure values up to 50 MPa. Additionally, this phenomenon can be applied in low temperature particle coating and processing of thermolabile substances such as proteins and peptides.
References


(24) BASF - Product Information BASF Chemicals NAFTA - Pluronic®


