

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 fluid¹. A supercritical fluid has liquid-like density and gas-like diffusivity which can also be tuned by varying operational temperature and pressure². 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 operations⁶⁻⁸.

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 moieties⁹⁻¹⁴. 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 fluoro 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 interactions⁸. 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.

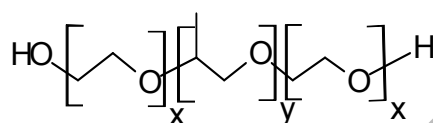


Figure 1: Generalized structure of a pluronic molecule; where x and y are positive integers

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 removed²⁰. 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 1.4²³.

Pluronic	Average Molecular weight ²⁴ (g/mol)	Melting point (K)	Average Weight EO	Average Weight PO	Average EO-units 2x	Average PO-units Y	EO:PO units
F-38	4600	321.15	3680	920	84	16	5.3 : 1.0
F-68	8400	325.15	6720	1680	152	29	5.2 : 1.0
F-108	14600	330.15	11680	2920	266	50	5.3 : 1.0
F-77	6600	321.15	4620	1980	106	34	3.1 : 1.0
F-127	12600	329.15	8820	3780	202	65	3.1 : 1.0

Table 1: Physical properties of Pluronics®

Pluronics® are generally regarded as safe (GRAS) and listed in the US and British Pharmacopoeia²⁵. They are widely used excipients as antifoaming agents, wetting agents, dispersants, thickeners and emulsifiers²⁶⁻²⁸. 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^{28,29}.

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^{3,19,30}. 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 %.

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

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

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3 pump attached to a 30 ml pressure vessel. A CCD camera with a fibre optic light source is
4 attached to the vessel and allows clear viewing of the vessel's interior. The pressure vessel
5 also contains an internal magnetic stirrer for effective mixing. Heating of the vessel is
6 controlled by an internal resistance thermometer up to a maximum temperature of 150 °C.
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8 Solid or liquid samples are placed in a glass capillary tube which is held securely on the
9 sample holder at the optimal viewing position.
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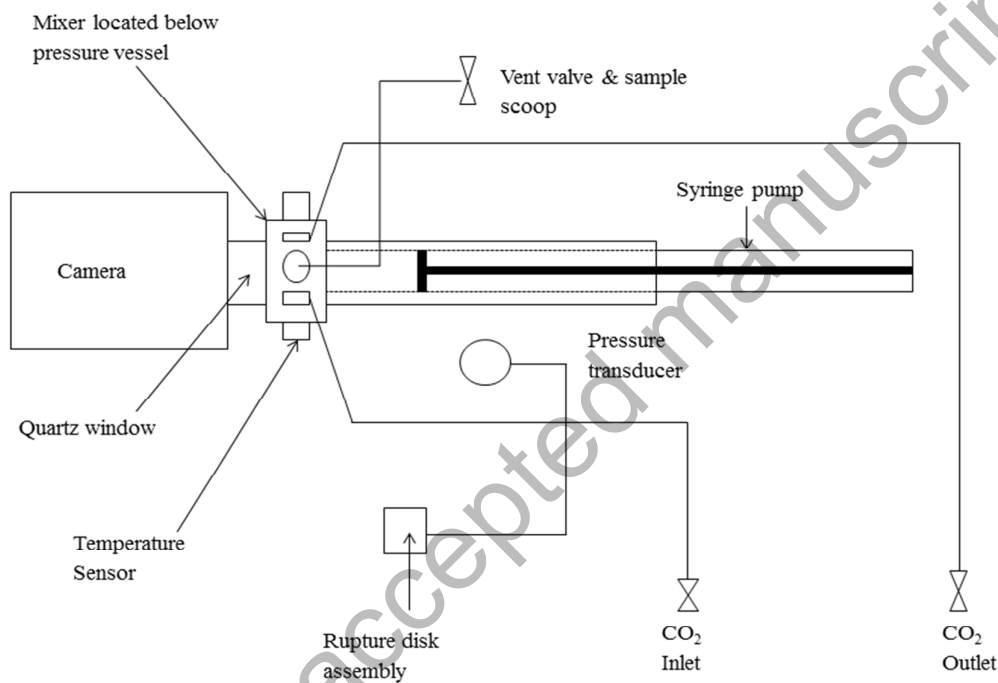
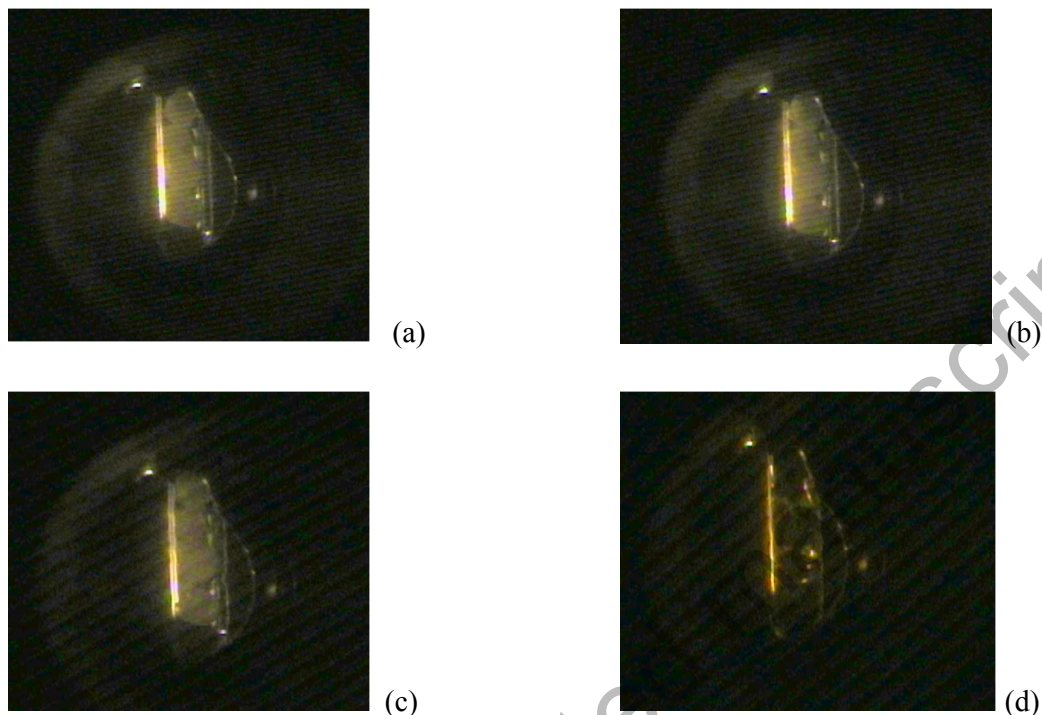


Figure 2: Schematic diagram of supercritical phase monitor

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

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3 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
4 were recorded in triplicate.
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31 Figure 3: Various stages of the experiment. [Pluronic F-68 at the; (a) Beginning of the experiment, (b)
32 After the introduction of CO₂, (c) Start of melting (d) Complete melt]
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35 **Powder X-ray Diffraction-** The diffractograms of the processed and unprocessed samples
36 were obtained using a D8 Advanced diffractometer (Bruker). Samples were analysed at room
37 temperature and in transmission mode using Mylar film for support. The samples were
38 rotated at 15 rpm and data was collected between 2.5 to 50° 2 θ , at a scan rate of 0.2°/s using
39 Cu K α radiation.
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44 **Differential Scanning Calorimetry-** The thermograms of processed and unprocessed
45 Pluronics® were recorded using DSC-1 calorimeter (Mettler Toledo). Samples (5-8 mg) were
46 weighed in standard aluminium pans and thermograms were recorded from 298.15 K to
47 378.15 K at heating rate of 10 K/ 60 s.
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51 RESULTS AND DISCUSSION

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54 The melting points of Pluronics® at atmospheric pressure were determined using DSC and
55 compared with their respective melting points in CO₂. Table 3 shows the melting temperature
56 of Pluronics® at atmospheric pressure (0.1 MPa) and at different pressure values in CO₂.
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Pressure (MPa)	Melting point mean (K) \pm Standard deviation (n=3)				
	F-77	F-127	F-38	F-68	F-108
0.1*	319.6	327.2	322.5	325.2	330.9
2.0	317.9 \pm 0.2	325.6 \pm 0.3	320.6 \pm 0.3	324.1 \pm 0.2	328.4 \pm 0.2
4.0	312.9 \pm 0.3	321.6 \pm 0.2	315.5 \pm 0.3	319.3 \pm 0.4	323.9 \pm 0.2
6.0	307.1 \pm 0.3	316.1 \pm 0.6	308.5 \pm 0.3	314.3 \pm 0.3	318.8 \pm 0.2
8.0	301.3 \pm 0.6	311.6 \pm 0.9	303.9 \pm 0.7	308.3 \pm 0.3	314.5 \pm 0.6
10.0	302.1 \pm 0.3	310.6 \pm 0.7	304.0 \pm 0.6	307.6 \pm 0.5	313.4 \pm 0.5
15.0	301.7 \pm 0.4	309.9 \pm 0.4	304.3 \pm 0.4	307.7 \pm 0.9	312.2 \pm 0.7
20.0	300.4 \pm 0.2	309.7 \pm 0.8	304.3 \pm 0.6	307.0 \pm 0.2	312.0 \pm 0.3
30.0	300.3 \pm 0.2	309.1 \pm 0.7	303.2 \pm 0.4	306.1 \pm 0.7	312.0 \pm 0.6
40.0	300.6 \pm 0.2	309.1 \pm 0.9	303.4 \pm 0.2	306.3 \pm 0.6	312.4 \pm 0.6
50.0	301.1 \pm 0.2	309.5 \pm 0.4	303.9 \pm 0.2	306.2 \pm 0.5	312.7 \pm 0.2

Table 3: Melting point of Pluronics® in CO₂ at different pressure values (* values determined by DSC)

The Pluronics® in CO₂ were found to melt at (18.1 \pm 0.5 to 19.3 \pm 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, respectively³¹. 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^{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 CO₂ 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^{7,33}. Similarly, recent studies have shown that ionic salts also demonstrate melting point depression in CO₂. Their melting behaviour was comparable to Pluronics® in the pressure range of 0.1 to 40 MPa^{34,35}.

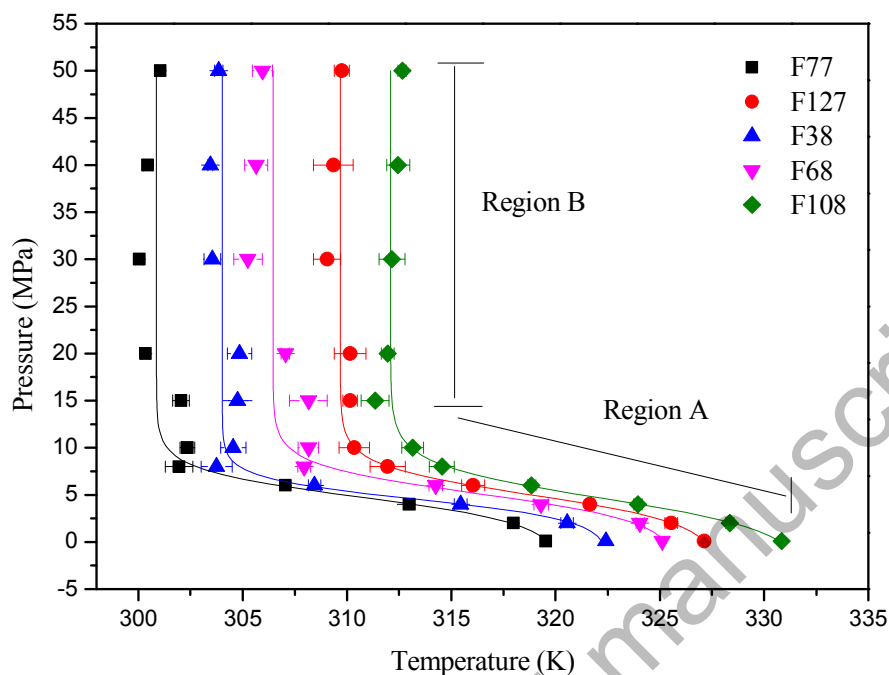
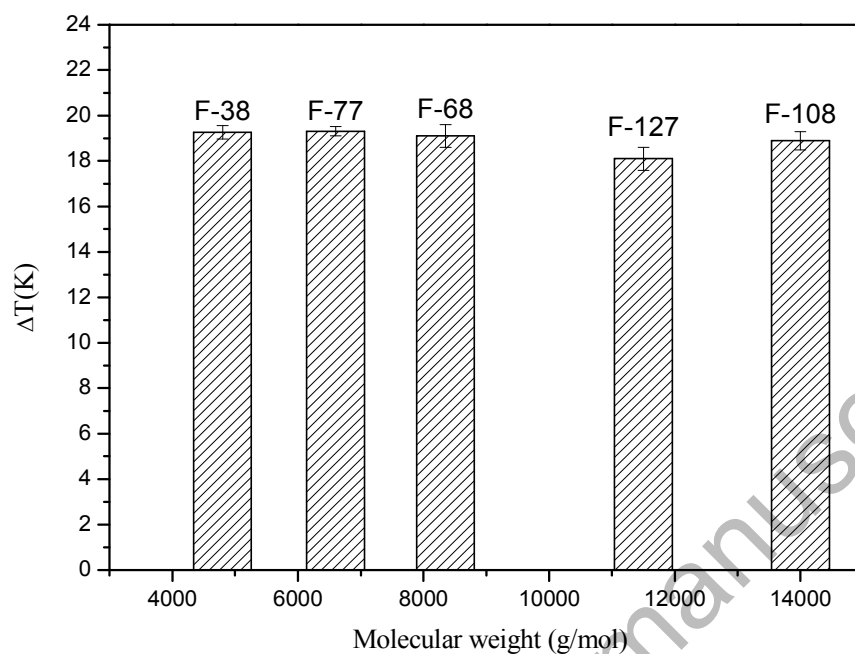
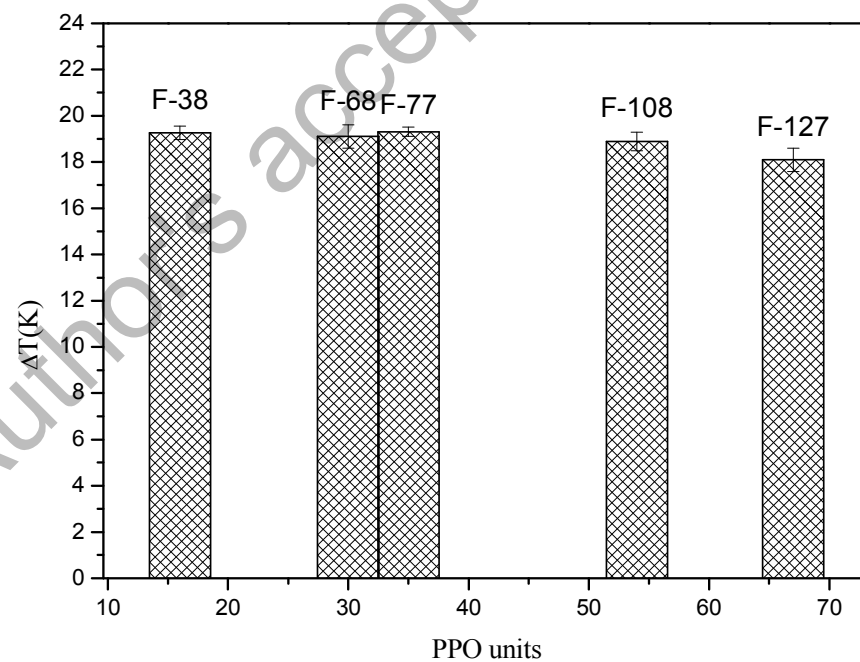


Figure 4: Melting temperature of Pluronic® at a pressure range of (0.1 to 50) MPa.

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 CO_2 in the matrix³⁶. The degree of depression is dependent on CO_2 's ability to interact with CO_2 -philic functional groups present in an excipient³⁷. Studies have shown that CO_2 -polymer mixing is favoured by the presence of carbonyl groups in polymers by Lewis acid-base interactions³⁰. Similarly, the presence of ether linkages in polymers has also shown to aid the CO_2 -polymer interactions, which depend upon the accessibility of ether oxygen³⁸. For example, it has been reported that PPO is relatively more CO_2 -philic than PEO. This is thought to be due to the weaker intermolecular forces in PPO because of an extra methyl group *per* monomer unit^{19,38}. This explains the solubility behaviour of small and medium molecular weight Pluronic® in CO_2 where increases in overall molecular weight and PEO content decrease its solubility¹⁹. The solubility of lower molecular weight (up to 3738 g/mol) Pluronic® decreases with the decrease in PPO/PEO ratio for a given molecular weight. Conversely, solubility of Pluronic® in CO_2 increases with the increase in molecular weight for a particular PPO/PEO ratio^{19,30}.



28 Figure 5: Comparison of melting point depression of Pluronic® with molecular weight
29 where, ($\Delta T = T_m$ measured by DSC - T_m at 30 MPa).
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56 Figure 6: Comparison of melting point depression of Pluronic® with PPO units
57 where, ($\Delta T = T_m$ measured by DSC - T_m at 30 MPa).
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3 Hence, it was expected that Pluronics® studied here with higher CO₂-philic PPO content
4 will show larger melting point depressions. However, Figure 5 and 6 suggest that the
5 interaction of CO₂ with Pluronics® was independent of PPO content and molecular weight.
6 This can be explained by the cohesive energy density of the polymers. It has been reported
7 that, as the number of favourable CO₂-polymer interactions increases, the enthalpy of mixing
8 may become more favourable whereas the entropy of mixing decreases³⁹. Increasing the
9 number of CO₂ interacting monomer units may also decrease the entropy of mixing by
10 hindering the segmental motion. This increase in monomer units is believed to enhance the
11 cohesive energy density of the copolymer only to an extent after which it may no longer
12 favour the enthalpy of mixing³⁹. Therefore, as the Pluronics® used in this study have large
13 numbers of CO₂- polymer interacting groups (ether linkages) corresponding to high cohesive
14 energy density such that the enthalpy of mixing is not favoured. This explains the similar
15 melting point depression for all studied Pluronics®.
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18 It is also important to note that the interaction of CO₂ with polymers is a complex
19 phenomenon which depends upon numerous factors like number and ease of accessibility of
20 CO₂-philic functionalities, polymer molecular weight, intermolecular bonding, structural
21 regularity, chain flexibility, copolymerization etc.⁴⁰. Therefore, more extensive studies
22 similar to this work at even higher pressure values are required to deduce the phase behaviour
23 of Pluronics® in CO₂.
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26 **Differential scanning calorimetric analysis**

27 DSC analysis was performed on CO₂ processed and unprocessed Pluronics®. The
28 thermograms presented in Figure 7 showed similar onset of melting/melting peaks for all
29 Pluronics®. Any appearance of a shoulder in the peaks was due to the presence of admixtures
30 of propylene oxide homopolymer with di or tri block copolymers⁴¹. Any difference in the
31 peak height was due to the sample size. This indicates that CO₂ processing had no effect on
32 thermal properties of Pluronics®.
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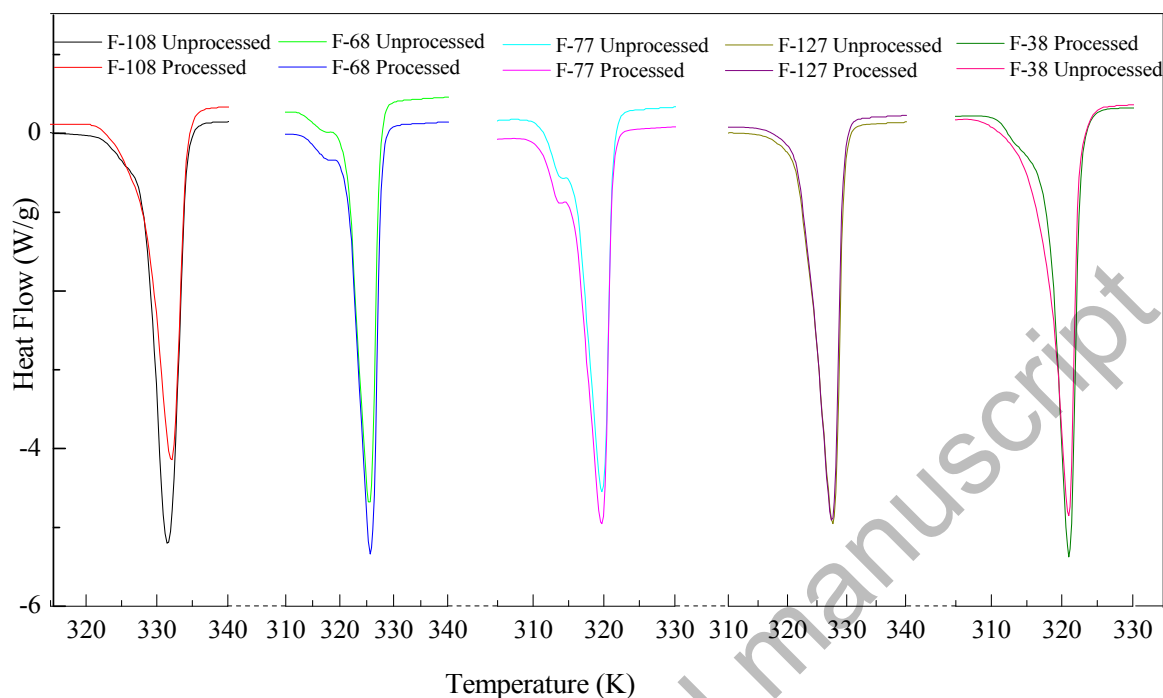


Figure 7: Thermograms of SCCO₂ processed and unprocessed Pluronics®

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 CO₂ processing. Peaks at 2θ 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 CO₂ 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 form²¹.

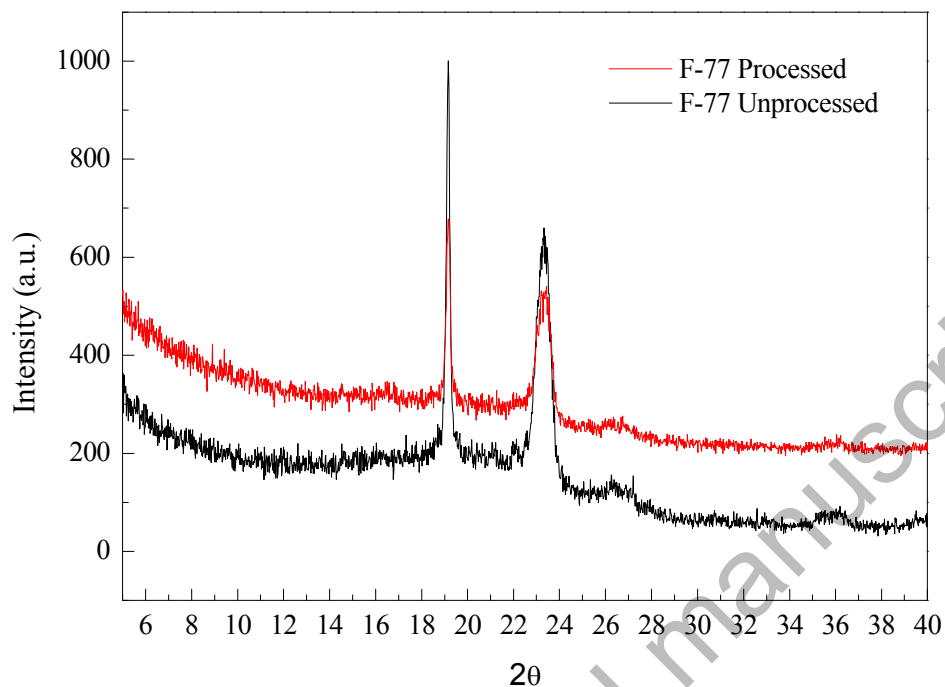


Figure 8: Diffractogram of processed and unprocessed pluronic F-77

Conclusions

In this study, it was observed that pluronic F-77, F-127, F-38, F-68 and F-108 melted at $(18.1 \pm 0.5$ to $19.3 \pm 0.3)$ 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.

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