Preparation and characterization of carbamazepine-polyethylene oxide hot-melt extruded solid dispersions

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Abstract

The aim of the present study was to investigate the possibility of usage of polyethylene oxide polymer (PEO, Polyox® WSR 301, Dow, USA) in the preparation of carbamazepine solid dispersions by hot-melt extrusion (HME). HME is a simple, solvent-free, continuous processing technique used to produce a variety of dosage forms. Thermoplastic materials, such as PEO polymers, are required for the process feasibility. Poloxamer 407 (Lutrol® F127, BASF, Germany) was used as a plasticizer to facilitate the HME process, by reducing the processing temperature and lowering the monitored torque. A hot-melt extruder with one rotating screw was used for the preparation of solid dispersions by HME technique (RCP-0250 Microtruder, Randcastle extrusion systems, USA), and physico-chemical properties of carbamazepine and polymers, their physical mixtures and dispersions made by HME were characterized by differential scanning calorimetry (DSC), thermo-gravimetric analysis (TGA), FT-IR spectroscopy and hot-stage microscopy (HSM) methods. Obtained results indicate that the addition of plasticizer enables preparation of carbamazepine-PEO hot-melt extrudates using a single-screw extruder configuration. It was demonstrated that there is no degradation of CBZ upon heating in the HME processing temperature range (90-110 °C). Furthermore, the crystalline form of CBZ was not altered during the HME processing. The presence of CBZ form III crystals, homogeneously dispersed in the hot-melt extrudates, was confirmed. Dispersion of CBZ crystals in the polymers mixtures was visualized using polarized light Hot-Stage Microscopy (HSM). Presented study demonstrates the potential of PEO 301 usage in the preparation of carbamazepine hot-melt extruded solid dispersions.

Keywords: carbamazepine, polyethylene oxide, hot-melt extrusion, solid dispersions

1. Introduction

Hot-melt extrusion (HME) is a simple technique widely used in the plastics, rubber and food industry; whereas its application in the field of pharmaceutical industry became more popular in the recent years. HME is a solvent-free, continuous processing technique used to produce a variety of dosage forms. During the hot-melt extrusion process, drug(s), binder and other excipients are fed into the heated barrel, mixed by the rotating screw element and extruded through the die attached at the end of the barrel. The materials inside the barrel are heated mainly by the heat generated due to the shearing effect of the rotating screw and the heat conducted from the heated barrel (McGinity, 2007). Due to intense mixing and elevated temperatures that are present during the processing, active ingredients are very uniformly dispersed in the hot-melt extrudates forming solid dispersions or solid solutions, depending on the miscibility with the binder selected for the extrusion process. Obtained extrudates can be transformed into powders by milling or cut to short lengths and then further pelletized. It has been proven that HME technology may improve the dissolution rate of poorly water-soluble drugs by forming solid dispersions and solid solutions (Perissutti, 2002), control or modify drug release (Follonier, 1994) and mask the bitter taste of drugs (McGinity, 2001).

Feasibility of the HME process requires the usage of thermoplastic binders – polymers, low melting point waxes, sugars or other polyols. Extrudable polymers and waxes, such as ethylcellulose, hydroxypropylcellulose, polyethylene glycols, polyethylene oxides, polymethacrylates, poly(vinyl acetate), carnauba wax, etc., are used most often. Properties of the binder used in the HME process influence both the processing conditions and the characteristics of the extruded dosage form (most importantly its stability and drug release).

Polyethylene oxide (PEO) polymers are semi-crystalline high molecular weight water-soluble polymers that can be used to produce variety of dosage forms. According to the manufacturer's (The Dow Chemical Company, USA) data, PEO polymers are well suited to thermoplastic processing, with the extrusion temperature ranging from 80 to 190 °C. Obtained extrudates exhibit modified drug release properties based on the polymer’s molecular weight. PEO polymers have been used to prepare hot-melt extruded chlorpheniramine maleate sustained release dosage forms (Zhang, 1999; Crowley, 2002), clotrimazole and nystatine films (Prodduturi, 2004; Prodduturi, 2007), ketoconazole films (Mididoddi, 2007), matrices for oral transmucosal delivery (Sridhar, 2008), solid dispersions of acetaminophene (Yang, 2010) and biculatamide (Abu-Diak, 2012). Cited references suggest that the HME processing of PEO polymers often requires inclusion of functional excipients, such as plasticizers and/or antioxidants in the extrudable formulation. This is done in order to improve processing conditions and/or to stabilize the final extruded product (McGinity, 2007). Plasticizers most often used in the HME process are citric acid and citric esters, low molecular weight polyethylene glycols, triacetin, phthalates, vitamin E TPGS, etc. (McGinity, 2007). Chlorpheniramine maleate was extruded with PEO using PEG 3350 as a plasticizer (Zhang, 1999). Vitamin E TPGS was included as an antioxidant in the HME films containing PEO and hydroxypropyl cellulose blends (Repka, 2000). It has also been demonstrated that lower molecular weight PEO polymers are more susceptible to degradation, when exposed to elevated temperature and pressure, in comparison to higher molecular weight polymers (Crowley, 2002). Poloxamer 407 is a copolymer of ethylene oxide and propylene oxide that has excellent suitability for the extrusion

process (Karl, 2011). It can be used as a plasticizer to facilitate the HME process, by reducing the processing temperature and lowering the monitored torque.
Carbamazepine (CBZ) is a white or off-white crystalline powder exhibiting polymorphism. Four anhydrous crystals forms of CBZ are known to exist: a P-monoclinic (form III), a triclinic (form I), a trigonal (form II) and a C-monoclinic polymorph (form IV) (Kipouros, 2006); with the form III being the polymorph used in commercial pharmaceutical formulations (Lefebvre, 1986; Davis, 2004). It is a widely used antiepileptic drug having narrow therapeutic index and relatively high plasma concentration variability (Martindale, 2007). Uniform dispersion of the drug and its controlled release profile from the dosage form are required in order to achieve desired therapeutic effect.
Therefore, the aim of the presented study was to investigate the possibility of usage of polyethylene oxide polymer in the preparation of carbamazepine hot-melt extruded solid dispersions, with the purpose of improving carbamazepine dissolution properties.

2. Material and Methods

Samples of carbamazepine (Ph. Eur. 7), polyethylene oxide polymer PEO 301 (Polyox® WSR 301, DOW, USA) and poloxamer 407 (Lutrol® F127, BASF, Germany) were kindly donated from suppliers. Citric acid and PEG 4000 (Ph. Eur. 7) were used as received. Physico-chemical properties of carbamazepine, plasticizers and polymer, their physical mixtures and dispersions made by HME were characterized in detail.

a. Preparation of physical mixtures

Physical mixtures were prepared by manually mixing carbamazepine (CBZ, polymorphic form III) and polyethylene oxide polymer at various drug-polymer ratios (1:9, 2:8, 3:7, 4:6, 5:5, 6:4, 7:3, 8:2, 9:1 % w/w), using mortar and pestle

Table 1 Composition of physical mixtures used in the study

Physical mixture	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	CP9
Composition (drug:polymer ratio)	1:9	2:8	3:7	4:6	5:5	6:4	7:3	8:2	9:1

b. Preparation of solid dispersions

A single screw hot-melt extruder was used for the preparation of solid dispersions by HME technology (RCP-0250 Microtruder, Randcastle extrusion systems, USA). Powder mixtures were fed into the extruder by gravitational flow. Four temperature zones of the extruder cylinder, from the feeding zone to the metering zone, were heated up to 90, 100, 105 and 110 °C, respectively. Rotational speed of the screw was adjusted to 25 rpm. The extrudates were collected after cooling at ambient temperature and manually cut in ~5 mm length pieces.

Table 2 Composition of the hot-melt extruded solid dispersions

Formulations	Composition (% w/w)		
	CBZ	PEO 301	Lutrol F127
CPL1	10	70	20
CPL2	20	60	20
CPL3	25	55	20
CPL4	25	60	15

c. Thermo-gravimetric analysis (TGA) and Differential scanning calorimetry (DSC)

Thermal analyses were carried out on a Shimadzu TGA-50 thermo-gravimetric analyzer, and a DSC-50 differential scanning calorimeter (Shimadzu Corporation, Japan). Non-isothermal experiments were performed in the temperature range 20 – 220 °C at a heating rate of 10 °C/min and under a nitrogen purge gas flow of 50 ml/min. The average sample size was 5 mg. Instruments were calibrated for temperature and energy using indium standards.

d. Fourier-transform infrared spectroscopy (FTIR)

FT-IR spectra in the region of 600 – 4000 cm^{-1} were obtained after appropriate background subtraction, using a Shimadzu IR-Prestige-21 FT-IR spectrometer coupled with a horizontal Golden-Gate MKII single reflection ATR system (Specac, Kent, UK) equipped with a ZnSe lense.

e. Hot-stage microscopy (HSM)

HSM was undertaken with a Kofler hot stage (Reichert Thermovar, Austria) equipped with a temperature controller (Jumo iTron 04, Germany) under a polarized light microscope Olympus BX 41 (Olympus, Japan). The microscope was equipped with a Leica DFC295 camera and controlled by the Leica Application Suite software (Leica Microsystems, Mannheim, Germany).

3. Results and Discussion

Thermal analysis of the pure drug substance demonstrated a characteristic CBZ form III thermogram (Figure 1) with three events, as reported previously (Kobayashi, 2000). The endothermic peak observed at 177.1 °C is attributed to the melting of the drug and involves a 19.26 J/g enthalpy change. This event is followed by an exothermic peak at 181.7 °C due to crystallization into form I, and the ΔH value calculated as the sum of these two events (6.33 J/g) represents the whole form III to form I transition. The third event observed at 193.7 °C (ΔH = 102.9 J/g) is due to melting of form I. Obtained results are in accordance with previous reports (Zerrouk, 2001).

PEO 301 polymer thermogram (Figure 1) shows one endothermic event (melting of the crystalline polymer) starting at 55.37 °C and reaching its peak at 71.95 °C, with the enthalpy change of 161.52 J/g.

There were no significant changes in the mass of materials' samples upon heating in the extrusion temperature range, according to thermogravimetric analysis. Thermal degradation of drug or excipients is, therefore, not expected in the hot-melt extrusion process.

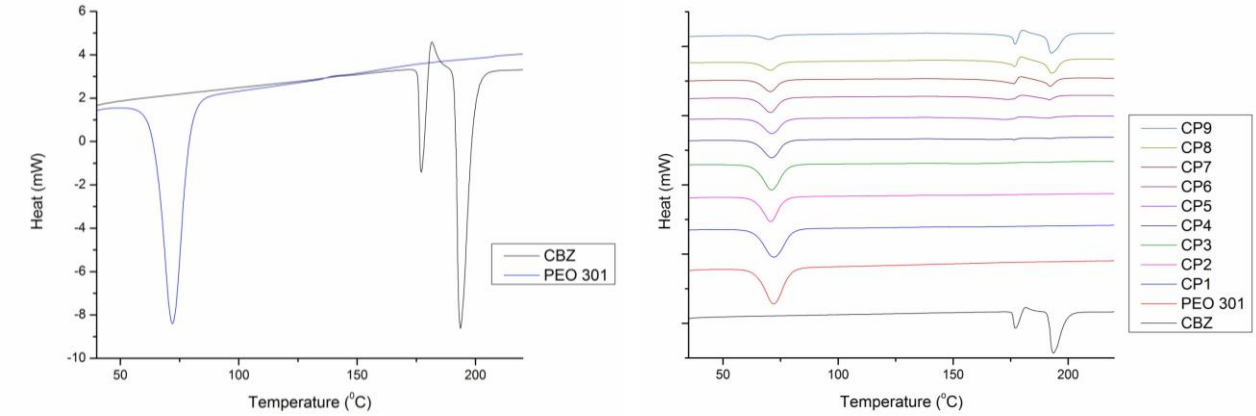

Figure 1 DSC thermograms of CBZ, polyethylene oxide polymer PEO 301 (left) and their physical mixtures (right)

Regarding physical mixtures, the DSC curves of samples containing up to 40 % w/w of CBZ exhibit only an endothermic peak corresponding to the polymer, whereas further increase in CBZ content in mixtures leads to amplification of CBZ melting peaks (Figure 1). Almost complete absence of CBZ peaks in polymer-rich samples can be attributed to excellent miscibility of the polymer and CBZ. Onset of form III melting is shifted towards somewhat lower temperatures, indicating favorable interaction of CBZ with molten polymer (Table 3), i.e. formation of solid dispersion.

Table 3 Thermal events associated with pure components and physical mixtures

Sample	CBZ	PEO 301	CP1	CP2	CP3	CP4	CP5	CP6	CP7	CP8	CP9
Onset of melting (°C)	174.3 189.3	55.37	55.66	52.49	53.47	55.76	53.92 142	54.93 141.1 180.7	56.76 142.6 181.5	60.57 146.3 181.4	60.6 150 184.7
Melting point (°C)	177.1 193.7	71.95	72.04	70.7	71.2	71.16	71.21 172.8	70.6 174 191.9	70.5 176.5 192.2	70.48 176.7 193.1	69.99 176.9 192.7
Fusion enthalpy (J/g)	19.26 102.9	161.52	147.89	127.49	115.39	97.17	82.47 26.85	72.92 30.34 16.06	54.63 30.54 27.38	33.21 24.82 44.34	17.72 24.13 70.56

In order to define phase diagram of CBZ-PEO 301 system, changes in onset of melting and melting points, as well as changes in the enthalpy of fusion were plotted versus mixture compositions. Obtained results indicate that CBZ and PEO 301 polymer are miscible throughout

a wide range of drug-polymer ratios. This observation is in accordance with the solubility parameter (δ) estimation, whereby compounds with a $\Delta\delta$ equal or less then 7.0 $MPa^{0,5}$ are likely to be miscible (Greenhalgh, 1999). Carbamazepine solubility parameter is 27.0 $MPa^{0.5}$ (Kolter, 2010), whereas solubility parameter of polyethylene oxide polymers is approximately 20.0 $MPa^{0.5}$ (Mieczkowski, 1991).

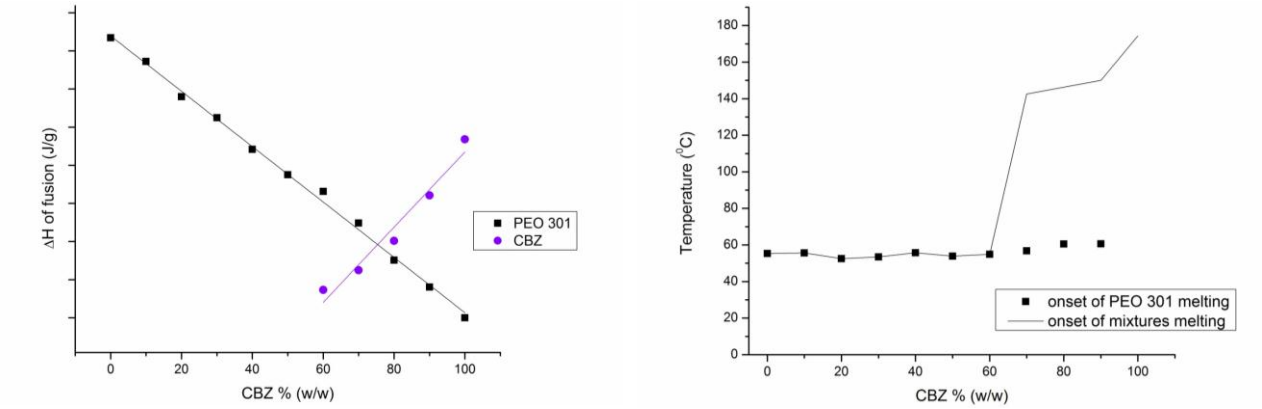

Figure 2 Phase diagrams of CBZ – PEO 301 mixtures

In order to verify the observations obtained by the DSC methodology, samples were heated on the hot-stage and observed under the polarized light microscope. Thermal changes occurring in physical mixture containing equal amounts of CBZ and PEO 301 are represented in Figure 3.

In order to investigate possible solid-solid interactions between CBZ and PEO 301 polymer upon mixing, FTIR spectra of the physical mixtures were recorded (Figure 4). FTIR spectra of the physical mixtures all have CBZ form III peaks in the studied spectral range; with the peaks being more pronounced with the increase in CBZ content in the mixture. FTIR spectra obtained for CBZ confirms form III characteristics reported in the literature (Grzesiak, 2003). Therefore, results indicate the absence of solid-solid interactions between the drug and polymer that could lead to a polymorphic transition.

Once the drug and thermoplastic polymer were characterized, hot-melt extrusion process was set up. PEO 301 polymer was not extrudable on its own using the single screw hot-melt extruder, within the temperature and speed of the rotating screw ranges tested. Microtruder RCP-0250 has a built-in pressure transducer that measures the pressure rise and stops the rotating screw element once the pressure reaches a critical value, in order to prevent damage. The viscosity of the molten mass in the extruder was probably too high for the single screw element to extrude it, therefore it was necessary to include a plasticizer in the formulation in order to facilitate the melt-extrusion process. PEG 4000 was first selected as the plasticizer, but with no effect on improvement of melt flowability in the extruder. When the mixture of citric acid and PEO 301 polymer (1:4 ratio) was extruded, recorded pressure went up to 1800 psi, whereas the mixture of poloxamer 407 (Lutrol F127) in the same polymer-plasticizer ratio was extruded at 900 psi pressure. Lutrol F127 was therefore selected as the plasticizer for further experiments. Settings for heating of the four temperature zones and screw speed were adjusted to obtain optimal flow into the barrel and uniform shape and appearance of the extrudates leaving the extruder die.

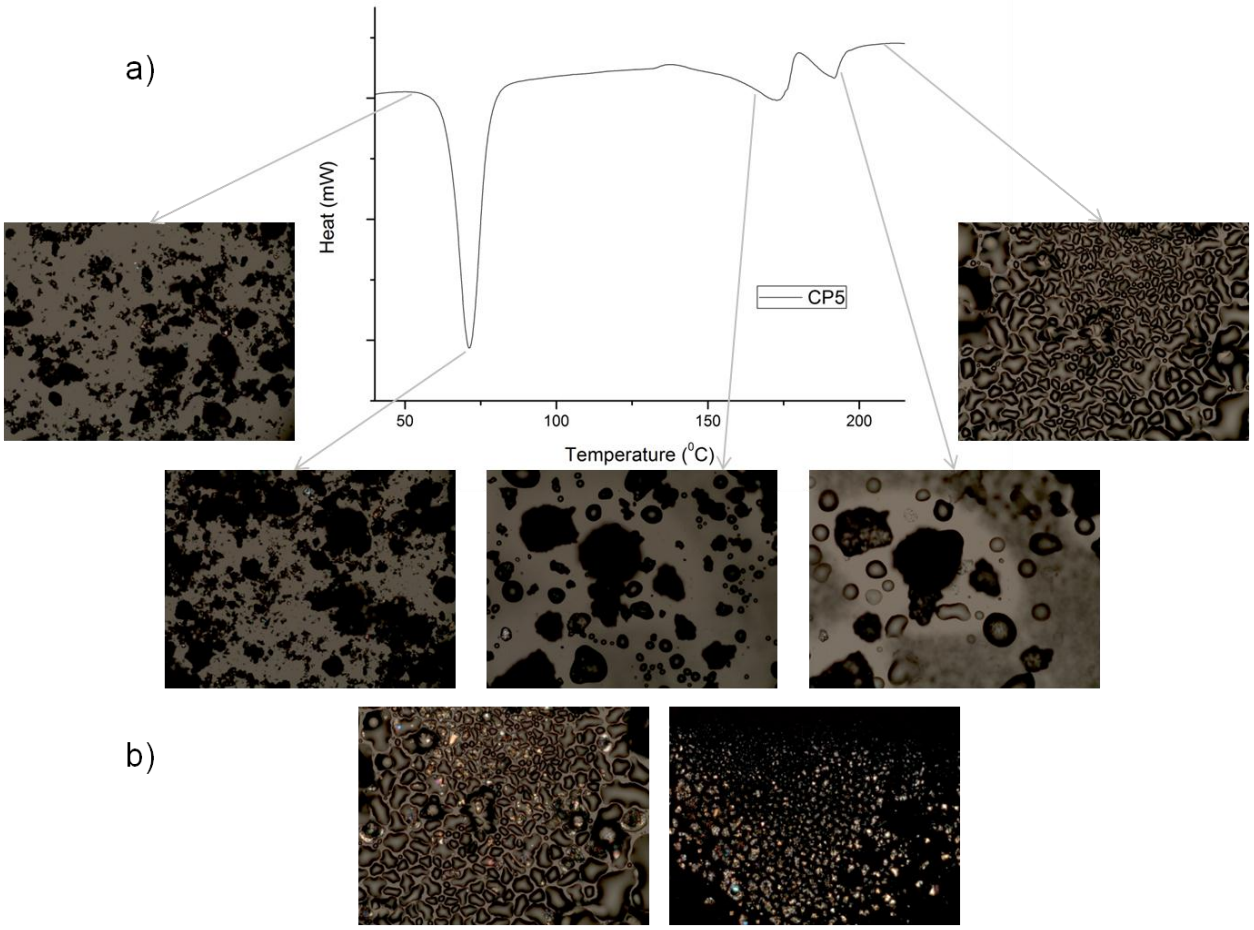

Figure 3 a) DSC thermogram of CP5, physical mixture composed of equal amounts of CBZ and PEO 301, thermal events are observed using the hot-stage polarizing microscope; b) crystallization is observed under the polarized light microscope upon cooling

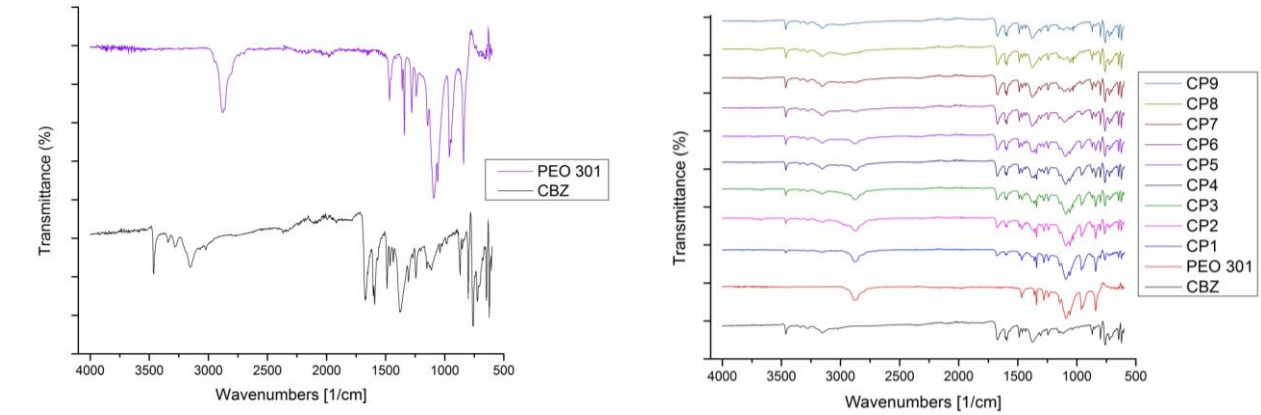

Figure 4 FTIR spectra of CBZ, polyethylene oxide polymer PEO 301 (left) and their physical mixtures (right)

Four different formulations were prepared (Table 2) and extruded using the hot-melt extruder. Pressure was monitored during the extrusion process, confirming the previous observations on influence of the plasticizer on melt flowability. Decrease in plasticizer concentration in 5 % led to increase in the pressure for up to 500 psi. Solid dispersions containing up to 25 % of carbamazepine could be extruded using the single screw hot-melt extruder.

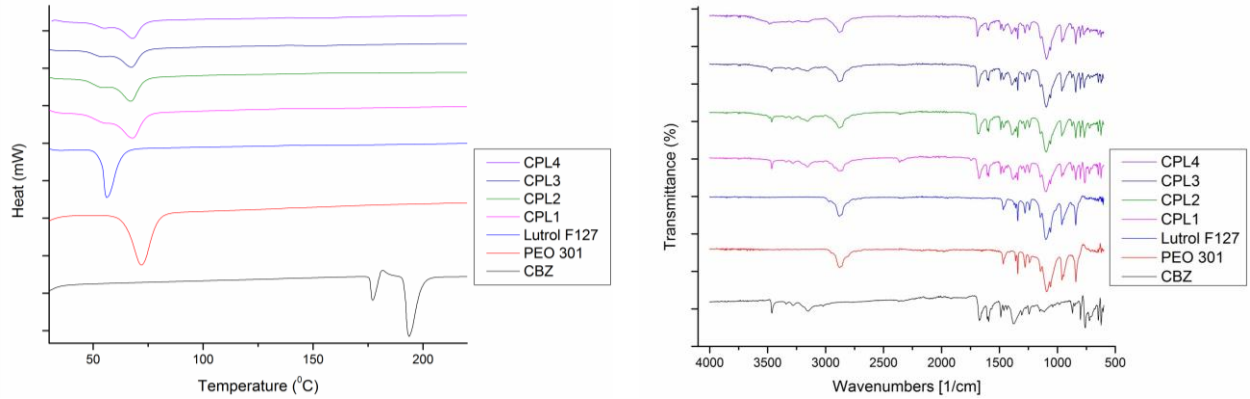

Figure 5 DSC thermograms (left) and FTIR spectra (right) of carbamazepine, PEO 301, Lutrol F127 and hot melt extrudates

Prepared extrudates were characterized in order to assess the state of dispersed carbamazepine. Presence of the plasticizer and the processing conditions do not affect carbamazepine – PEO 301 miscibility, and carbamazepine has remained in its form III crystalline state (Figure 5) in the hot-melt extrudates. Melting of CPL4 formulation (containing 25 % of carbamazepine, 15 % of Lutrol F127 and 60 % of PEO 301 polymer) was performed on the hot-stage and the crystallization upon cooling was observed under crossed polarizers (Figure 6). Formation of crystalline dispersion upon cooling was confirmed.

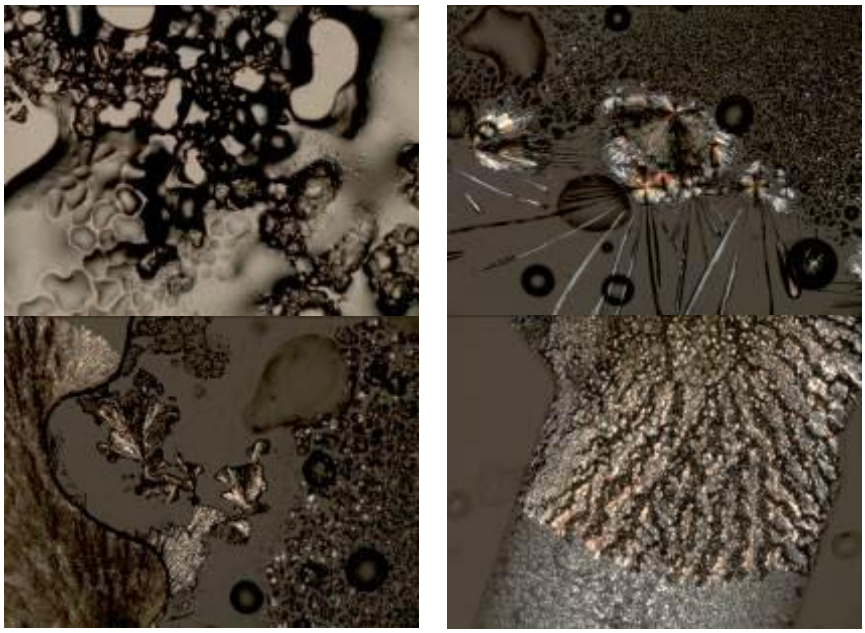

Figure 6 Melting of CPL4 formulation (top left), followed by the onset of crystallization (top right and bottom left) and formation of crystalline dispersion (bottom right)

4. Conclusion

Results of the presented study demonstrate the potential of PEO 301 application in the preparation of carbamazepine hot-melt extruded solid dispersions using the single screw hot-melt extruder. Crystalline dispersions of carbamazepine form III were formed. Hot-melt extrusion is, therefore, an efficient technology for continuous solvent-free preparation of carbamazepine solid dispersions.

5. Acknowledgments

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