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Interactions of topiramate with polyethylene glycol 8000 in solid state with formation of new polymorph

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ABSTRACT

Topiramate [2,3:4,5-bis-O-(1-methylethylidene) β-D-fructo-pyranose sulfamate] was found to form a new polymorphic form in the presence of polyethylene glycol 8000 (PEG). Comparative study of the solid state interactions of PEG and structural topiramate analogue lacking sulfamate group (Diacetone D-fructose) indicated that the sulfamate moiety was essential for the formation of the new polymorph. The drug–polymer interactions were investigated using differential s canning calorimetry (DSC), Fourier Transform Infrared Spectroscopy (FTIR) and hot stage microscopy. The new polymorphic form was characterized using variable temperature powder X-ray diffraction (VTPXRD) and solid state Nuclear Magnetic Resonance (ssNMR). The new polymorph was found to form only in the presence of PEG at specific weight ratios.

1. Introduction

Solid-state interactions of active pharmaceutical ingredients and polymers play an important role in pharmaceutical product development. The outcomes of these interactions often result in the change of a drug dissolution rate and may have a profound impact on product stability (Newa et al., 2008). The drug–polymer interactions are often explained by the changes in the hydrogen bonding networks, and may lead to complexation or polymorphic transformations (Naima et al., 2001). Understanding the polymorphic relationships is crucially important, as it provides basis for changes in dissolution rate, packing and melting behavior (Brittain, 1999; Suitchmezian et al., 2008). Theoretical studies of polymorphism usually focus on thermodynamic stability of different crystal forms (Hilfiker, 2006; Burger and Ramberger, 1979; Giron, 1995; Liu, 2000). Various predictive models have been proposed based on the intra- and intermolecular bonding to determine the energy range of possible polymorphism. The actual polymorphism screening studies largely remain empirical due to the limitations in the theoretical and computational approaches (Barnett et al., 2008; Price, 2008).

Topiramate [2,3:4,5-bis-O-(1-methylethylidene) β-D-fructo-pyranose sulfamate] is a broad-spectrum antiepileptic drug used for treatment of seizures and migraine prevention (Nortey et al., 1997). It is currently marketed by Ortho-McNeil-Janssen Pharmaceuticals, Inc. under the trade name Topamax® as tablets and sprinkle capsules. Topiramate is a sugar sulfamate derivative with relatively high aqueous solubility (9.8 mg/ml) and low dissolution rate. The solid state characteristics and physicochemical properties of topiramate were reported in literature, however none of these studies pointed to the existence of topiramate polymorphs (Maryanoff et al., 1993; Sena et al., 2008). The crystal structure of topiramate was reported by Kubicki et al. in 1999. It was shown that the hydrogen bonds connected molecules of topiramate into sixth-order rings. The hydrogen bond-induced conformation was shown to be responsible for the mutual disposition of the hydrophilic and hydrophobic parts of the molecule.

Polyethylene glycols (PEG) are polymers with excellent biocompatibility and exhibit a combination of hydrophilic and lipophilic properties. These properties make them highly useful in enhancing the solubility of various active compounds, such as phenylbutazone, paracetamol, indomethacin, hydroflumethiazide and bendrofluazide (Corrigan et al., 1979; Leuner and Dressman, 2000). Depending on their molecular weight, PEG polymers exist as viscous and colorless liquids (molecular weight below 100 Da) to waxes and highly crystalline solids (molecular weight of up to 10,000,000). The melting points (m.p.) of polyethylene glycols are related to their molecular weights and range from 3 to 68 °C (Bailey and Koleske, 1976).

The physicochemical interactions of polyethylene glycols with various active ingredients have been extensively studied, and their behavior in solid state and in solution has been characterized (Chang et al., 1975; Hua et al., 2005; Venuti et al., 2000). Several indications of crystal form transitions in presence of polyethylene glycol have been previously reported for nimodipine, carbamazepine and flurbiprofen (Docoslis et al., 2007; Lacoulonche et al.,

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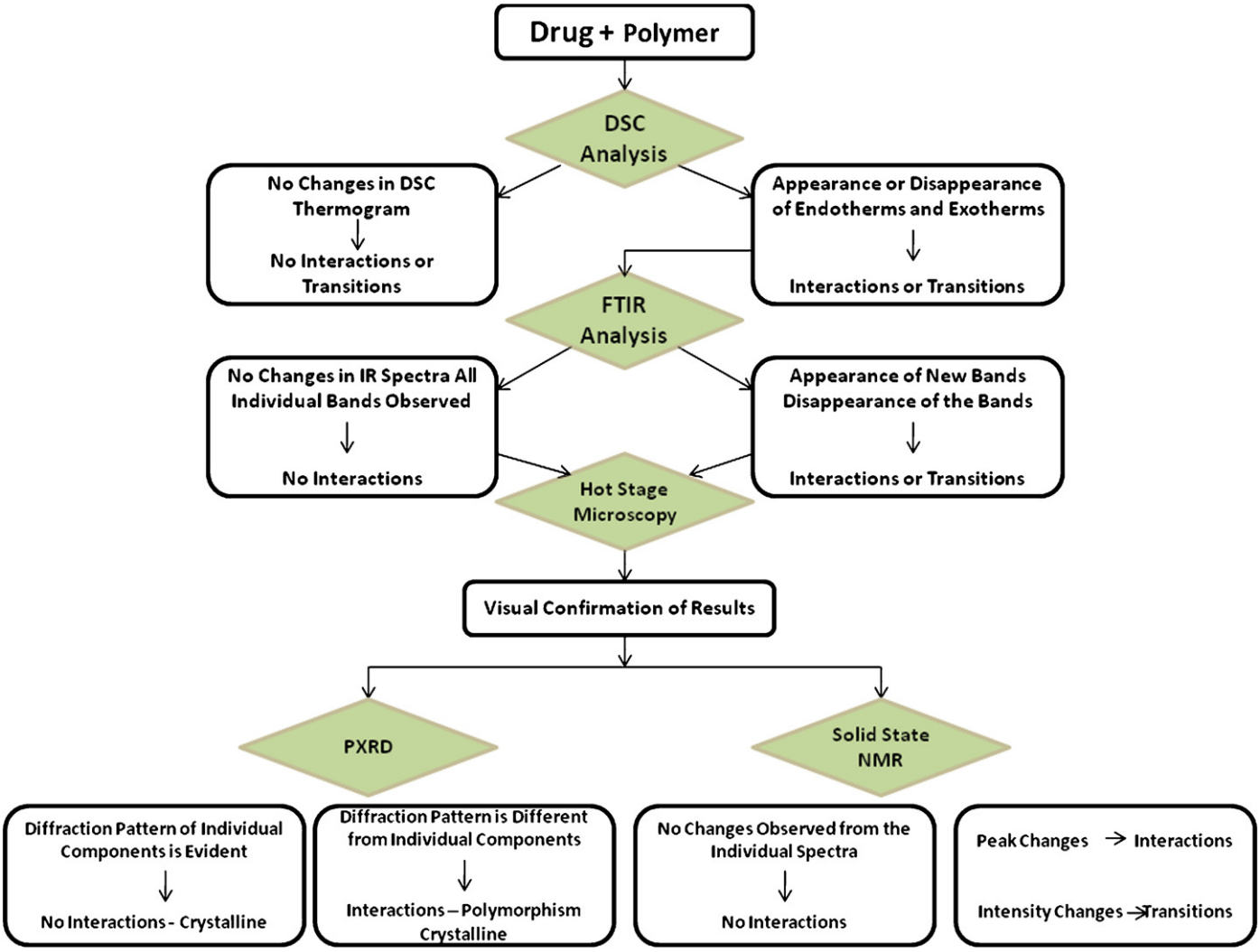

Fig. 1. Schematic characterization of drug/polymer interactions.

1998; Naima et al., 2001). The described crystal form changes included amorphous-crystalline conversions and new polymorph formation, which were commonly attributed to changes in hydrogen bonding as a result of the drug–polymer interactions.

Characterization of solid state transitions is a complex process often requiring more than one technique to provide conclusive evidence of the changes. A schematic typically used for characterizing the drug/polymer interactions is illustrated the Fig. 1. While the initial indication of the solid state transitions could be detected and visualized by the thermal methods of analysis (differential scanning calorimetry and hot stage microscopy), these methods would not distinguish between the chemical interaction and the physical form changes. Infrared spectroscopy can provide distinction in such cases. If no evidence of the chemical interaction is found, the crystal form transitions may be characterized conclusively using the crystallographic methods and solid state nuclear magnetic resonance spectroscopy. In this investigation, multiple methodologies were used to study the interactions between polyethylene glycol and topiramate in solid state.

2. Experimental

Topiramate (m.p. 128 °C) and Diacetone-D-fructose (m.p. 93–96 °C) (Fig. 2) used for these experiments were donated by Johnson & Johnson Pharmaceutical Research & Development, L.L.C., Raritan, NJ. Initial variable temperature powder X-ray diffraction (VTPXRD) and solid state NMR (ssNMR) analysis confirmed it to be the known form of topiramate. Polyethylene glycol 8000 (m.p. 61–62 °C) (Fig. 2) was obtained from Dow Chemical Co. (Danbury, CT).

2.1. Preparation of binary mixtures

Binary mixtures of topiramate and polyethylene glycol 8000 in the range of 5–95% (w/w) were prepared by weighing the components into a synthetic sapphire mortar and grinding them with a pestle for two minutes at room temperature.

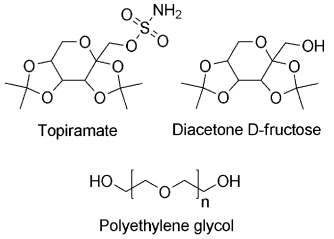

Fig. 2. Structural formulas of topiramate, diacetone-D-fructose and polyethylene glycol.

2.2. Differential scanning calorimetry (DSC)

Samples of 2–7 mg of binary mixtures prepared as described above were weighed and analyzed in hermetically sealed aluminum pans. Differential Scanning Calorimetry (DSC) was performed using a Q1000 DSC (TA instruments, New Castle, DE) calibrated with indium and scanned in the temperature range of −50 °C to 150 °C.

2.3. Hot stage microscopy (HSM) and polarized light microscopy

Polarized light microscopy was performed using a Zeiss Axioplan microscope fitted with a Zeiss Axiocam type 1 SNO641 digital camera (Zeiss, Thornwood, NY). Variable temperature experiments were conducted using an Olympus BX51 polarized light microscope (Olympus, Center Valley, PA) with the Linkam TMS94 hot stage unit (Linkam Scientific Instruments Ltd., Surrey, United Kingdom). Topiramate powder was placed on a slide next to the PEG powder to form the boundary where some of the particles came into direct contact. Samples were sealed in the hot stage plate and heated at the rate of 10 °C/min.

2.4. Attenuated total reflectance fourier transform infrared spectroscopy (ATR-FTIR)

Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR) of solid phases was performed using Nexus 470 FT-IR (Thermo Fisher Scientific Inc., Waltham, MA) with diamond crystal Smart OrbitTM ATR and Omnix software. Approximately 5 mg of each sample was placed on an ATR crystal accessory, and 32 scans were collected for each sample at a resolution of 4 cm^{-1} over a wavenumber region of 4000–600 cm^{-1}.

2.5. Solid state nuclear magnetic resonance (ssNMR)

Solid State Nuclear Magnetic Resonance (NMR) spectroscopy was performed on a Varian NMR System (Varian Inc., Palo Alto, CA) at 400 MHz with a Chemagnetics 4 mm triple resonance CPMAS probe. The ^{13}C cross-polarized spectra were obtained over the temperature range of 20–70 °C with samples spinning at 15 kHz.

2.6. Powder X-ray diffraction (PXRD)

Variable temperature PXRD was obtained using a Bruker AXS D8 Advance X-ray Diffractometer equipped with a SOLEX detector, Göbel Mirror and MRI Environmental Chamber. The temperature was varied from 30 °C to beyond the melting point of the substance in 10 °C increments. Scans were taken every 0.02° 2-θ for 0.6 s/scan. PXRD diffraction patterns were visualized using the EVA software package (Bruker, Madison, WI).

3. Results and discussion

3.1. Interactions in binary mixtures of topiramate and PEG 8000

Thermal analysis of the binary co-ground mixtures of topiramate with PEG 8000 by DSC showed the depression of the polymer melting point, suggesting the formation of eutectic or monotectic system. The topiramate melting point decreased as per the van't Hoff equation (Law et al., 2002). Surprisingly, the mixtures with high topiramate concentrations (50 and 75%, w/w) showed an additional thermal event with a melting onset at 80 °C (Fig. 3), indicating potential crystal form changes or interactions. To identify the region in which the changes occured, a phase diagram was constructed using the DSC scans of the co-ground binary mixtures of topiramate with PEG 8000 (Fig. 4). The phase diagram demonstrated presence of the changes in all mixtures with up to 60% polyethylene glycol (w/w).

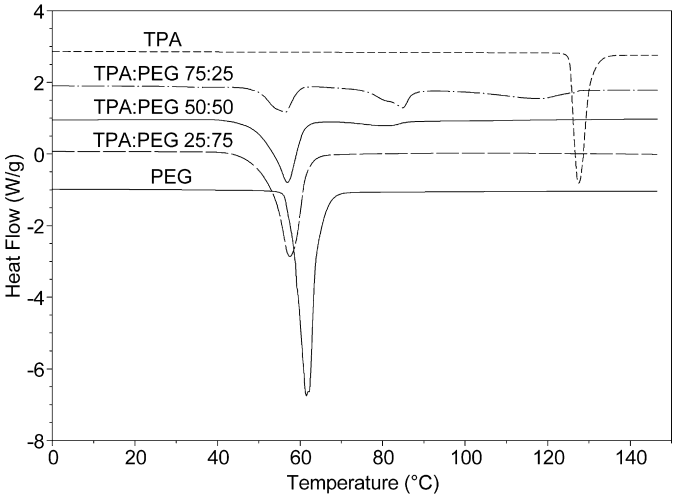

Fig. 3. DSC thermograms of Topiramate-PEG 8000 blends.

Thermal events in physical mixtures of polyethylene glycol 8000 with topiramate were visualized using hot stage microscopy. Simultaneous melting of the eutectics and crystallization to a new form was observed at the topiramate/PEG 8000 boundary at 55 °C, followed by the melting of the new crystal form that occurred at 80 °C (Fig. 5). Both photographs were taken from the sample placed in the same location at 200× magnification.

To investigate the new crystal form with the melting onset at 80 °C, a structural analogue of topiramate lacking the sulfamate group, diacetone-D-fructose (Fig. 2), was characterized using the same methodology as topiramate. Thermal analysis of the binary mixtures of polyethylene glycol 8000 with diacetone D-fructose (Fig. 6) showed a melting point depression indicative of eutectic formation, but no additional thermal events at any polymer concentrations. The XRD for the 50:50 (w/w) mixture (Fig. 7) confirmed that diacetone D-fructose did not undergo a crystal form transition in presence of the polymer. It was concluded that sulfamate group of topiramate was responsible for the interactions or transitions that occurred in the solid state mixtures of Topiramate and PEG.

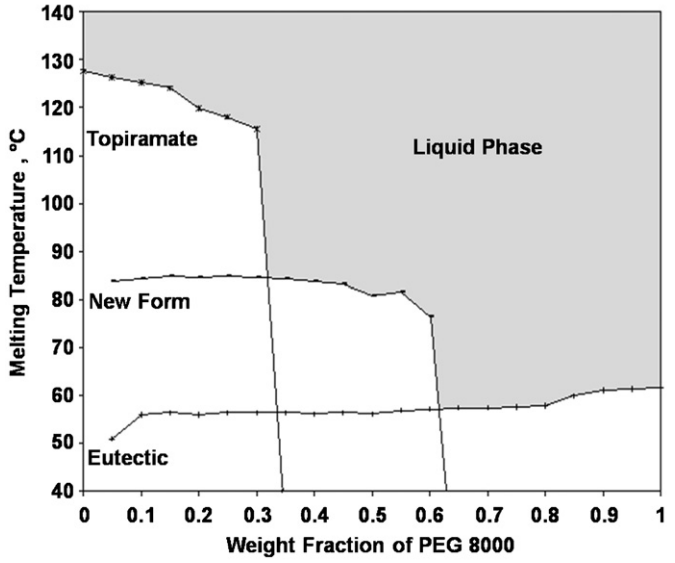

Fig. 4. Phase diagram for topiramate-PEG binary mixtures.

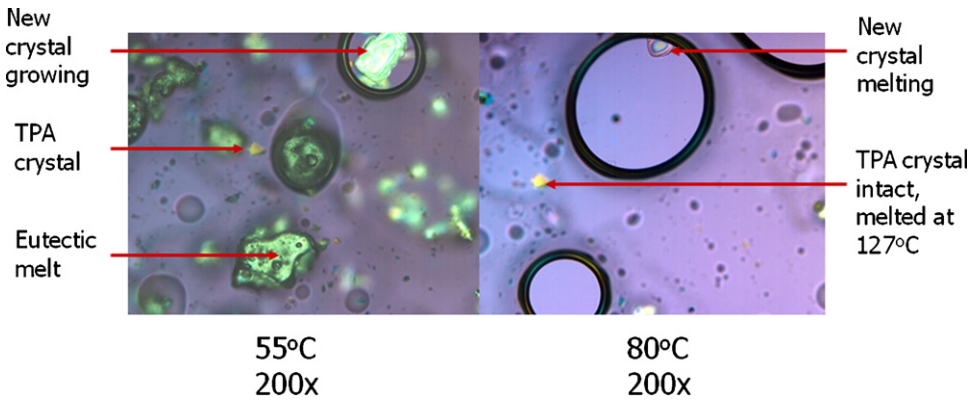

Fig. 5. Hot stage microscopy of PEG 8000 and topiramate: formation and melting of the new crystal form.

The potential complexation or lack thereof for the topiramate and PEG 8000 mixtures was examined using ATR-FTIR spectroscopy. The infrared peaks corresponding to each functional group in the individual compounds were assigned based on available literature (Kaushal et al., 2008 and Sena et al., 2008). The IR spectral bands related to the N–H vibrations of the sulfamate group in the spectral range of 3000–3500 cm^{-1} (not obscured by the PEG 8000 absorption) were followed to characterize the interaction. The band at 3376 cm^{-1} corresponded to the asymmetric N–H stretching vibration of sulfamate group. The band of symmetric stretching N–H vibration exhibited a double structure with components at 3242 and 3204 cm^{-1}. The band at 3108 cm^{-1} is an overtone of the N–H bending vibration at 1576 cm^{-1}. The examination of the ATR-FTIR results of the physical mixtures in the spectral range of 3000–3500 cm^{-1} showed that the mixture spectra in this region were equivalent to the spectra of pure topiramate (Fig. 8). The difference in the topiramate in the binary mixture resulted in variable peak intensities. The presence of all topiramate peaks in all physical mixtures including those containing the new crystal form indicated that no complexation occurred between drug and PEG 8000.

Based on the lack of the complexation between the Topiramate and the PEG, it was hypothesized that the observed crystal form is a new polymorph of Topiramate and that the polymorphic transition could be attributed to the rearrangement of the hydrogen bonding network of the sulfamate group of the drug. The solid state NMR and variable temperature XRD studies were conducted to confirm this hypothesis. Although multiple PEG-Topiramate com-

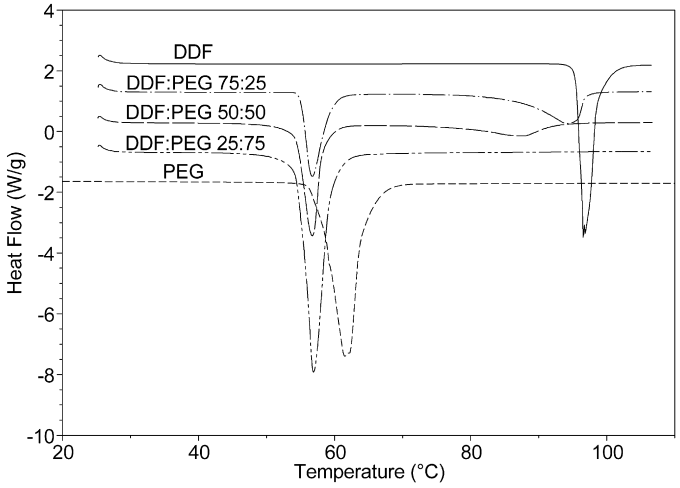

Fig. 6. DSC thermograms of diacetone-D-fructose – PEG 8000 co-ground mixtures with different weight ratios shows no crystal form changes.

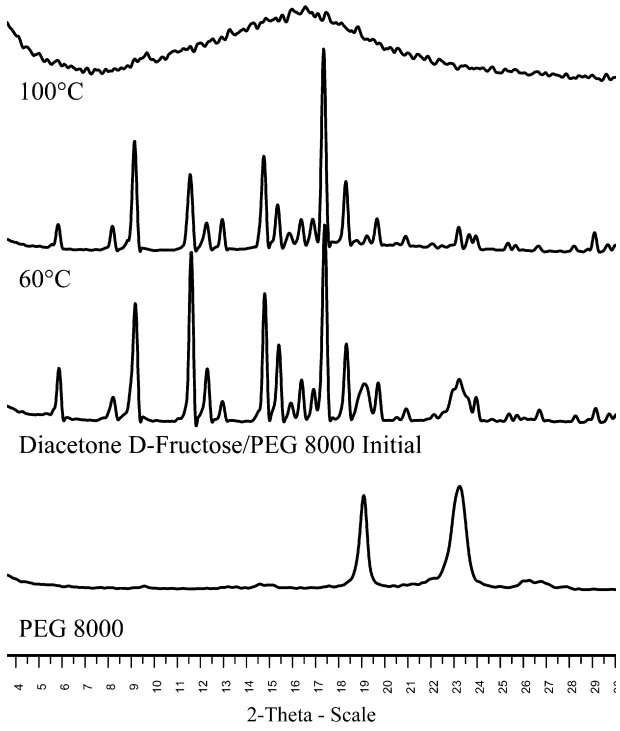

Fig. 7. VT-PXRD spectra of the 50:50 (wt:wt) mixture of diacetone-D-fructose and PEG 8000 shows no polymorphic transitions.

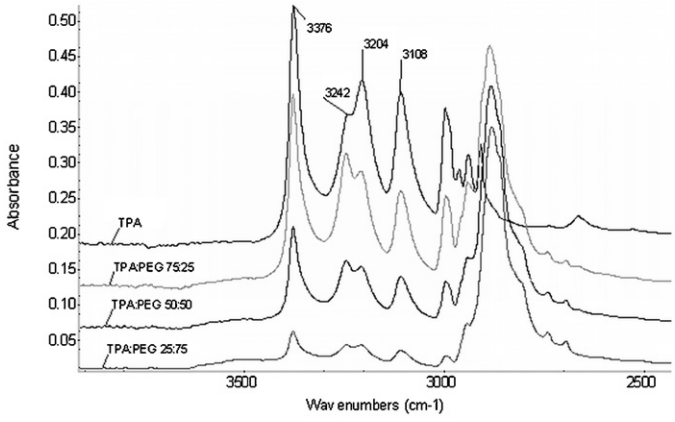

Fig. 8. ATR-FTIR spectra of topiramate (TPA) and binary mixtures of TPA with PEG 8000 (PEG).

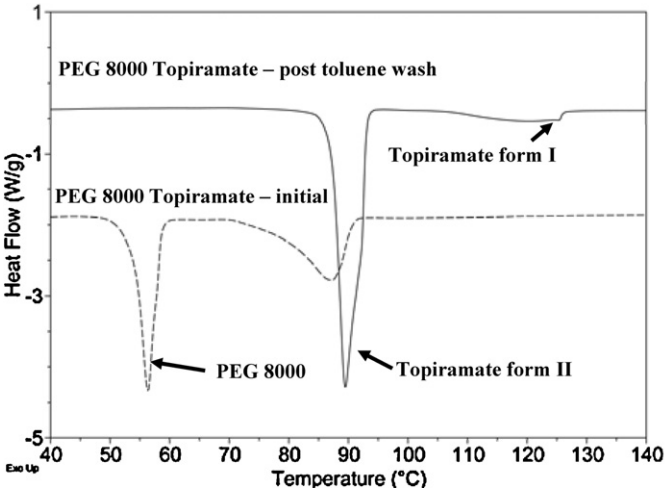

Fig. 9. DSC thermograms of Topiramate-PEG 8000 before and after washing with toluene indicating complete removal of PEG 8000 and minor conversion from topiramate form II to form I.

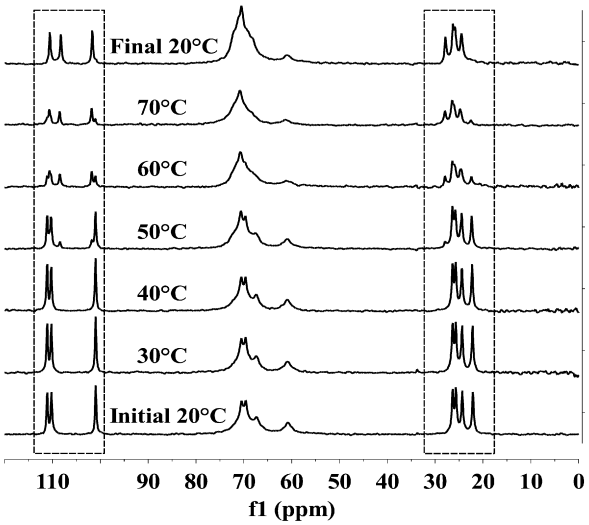

Fig. 10. ^{13}C SSNMR spectra of topiramate form I and PEG 8000 as a function of temperature.

positions showed reproducible formation of a new crystal form, isolation of the pure new crystal from the excess PEG 8000 was not feasible. The new form was found to be physically stable at ambient conditions for up to 4 months in the presence of PEG 8000. A series of experiments were conducted to compare the relative solubility of PEG 8000, topiramate and new crystal form in different solvents as a function of temperature. It was determined that PEG 8000 had a much higher solubility at elevated temperature in toluene than either topiramate or the new crystal form, and therefore toluene would likely be a suitable wash solvent. DSC confirmed that samples washed with warm toluene removed the excess PEG 8000, but still caused partial reversion of the new form to the original crystal form of topiramate (Fig. 9).

3.2. Characterization of the new crystal form of topiramate

As observed in the DSC thermograms, in the presence of topiramate, PEG 8000 melted below the melting point of pure polymer. Conversely, in the presence of PEG 8000, topiramate at above 50% in the mixture, formed a new crystal form with the melting onset at 80 °C, considerably below the topiramate melting point of 128 °C.

Polymorphic transition of topiramate form I to form II was studied by solid state NMR. The ^{13}C CPMAS NMR spectra of an equal-weight mixture of topiramate form I and PEG 8000 at 20, 30, 40, 50, 60, and 70 °C and after cooling to 20 °C is shown in Fig. 10. When the blend temperature exceeded 50 °C, peaks corresponding to the new crystal form of topiramate started to grow while the peaks corresponding to the initial topiramate crystal form started to decrease. By the end of the run, the new peaks increased and only faint original peaks were observed. A comparison of the ^{13}C CPMAS NMR spectrum of topiramate form I and form II shown in Fig. 11 indicated that the peaks present in form I and form II are identical suggesting that they are chemically same.

Variable Temperature XRD was used to confirm that the crystalline material was indeed a new form (Fig. 12). At room temperature the PXRD pattern of a 50:50 (w/w) mixture of topiramate form I and PEG 8000 had all the peaks seen in the individual components. The crystal form change was detected at 50 °C, as evidenced primarily by the presence of new peaks at 11.5°, 13.4°, 14.0°, and 16.4° 2θ and disappearance of the peaks at 13.0° and 15.3° 2θ. The broad peaks at 19.1° and 23.3° 2θ due to crystalline PEG 8000 have disappeared by 70 °C, at which point the PXRD pattern for pure topiramate form II could be clearly seen. At 90 °C, the entire sample became amorphous as shown by PXRD pattern, indicating no crystalline topiramate form I was present.

In summary, formation of the new metastable polymorph of topiramate in presence of the polymer, PEG 8000, has been demonstrated by DSC, hot stage microscopy, variable temperature XRD and solid state NMR. It was shown that while formation of the eutectic systems was common for both topiramate and diacetone-D-fructose, the formation of a new form required the presence of the sulfamate group. In addition, other compounds that are known to exhibit polymorphic transitions in presence of polyethylene glycols contain the functional groups that behave similarly to the sulfamate entity in presence of the polymer. For example, Naima et al. (2001) reported the polymorphic transition of carbamazepine in its binary mixtures with PEG 6000. Similar to topiramate, transformation of the stable carbamazepine polymorph III to the metastable polymorph II occurred in liquid phase upon formation of eutectic system. The geometry of the amide group of carbamazepine is known to be responsible for stabilization of its polymorphic configurations: all four known polymorphic forms of this compound are stabilized by the hydrogen-bonding motifs (Cabeza et al., 2006; Krahn and Mielck, 1989). Likewise, the changes in crystal form of topiramate were related to the rearrangement of the hydro-

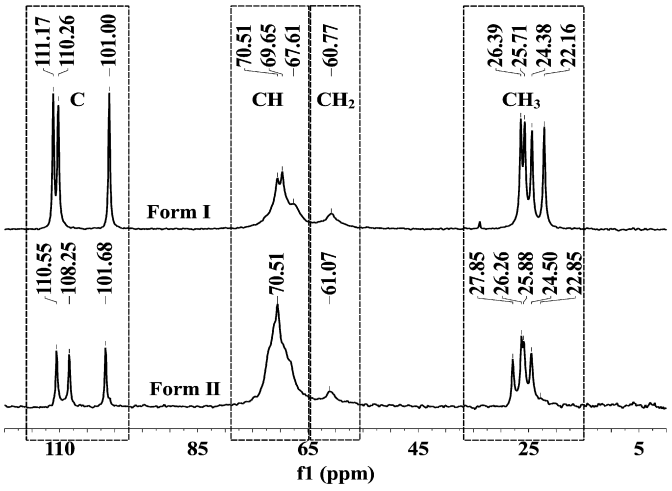

Fig. 11. Comparison of the ^{13}C CPMAS NMR spectra of topiramate form I and form II.

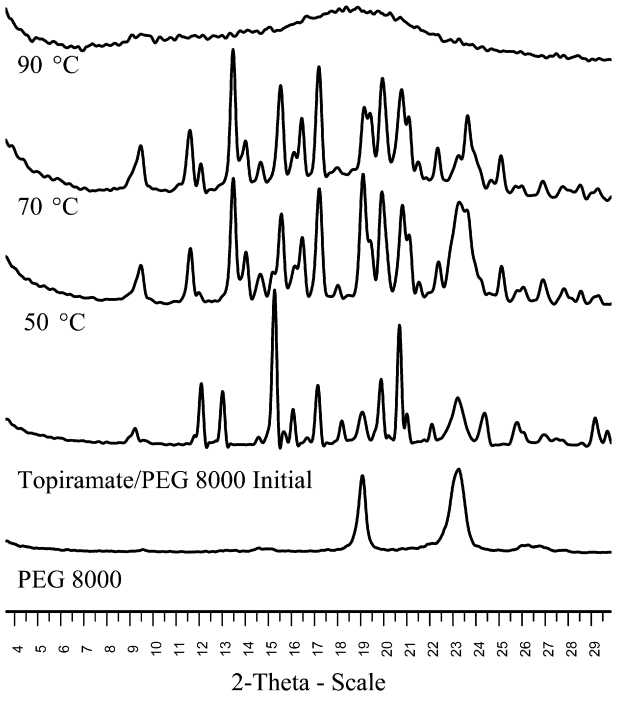

Fig. 12. Variable temperature PXRD of 50:50 (w/w) topiramate form I and PEG 8000.

gen bonding network of the sulfamate groups in presence of the polymer.

4. Conclusions

This study demonstrated formation of a new polymorphic form of topiramate in presence of polyethylene glycol 8000. The polymorphic transition has been confirmed by DSC, hot stage microscopy, solid state NMR and PXRD. The comparative study of topiramate with its structural analogue lacking the sulfamate moiety (diacetone-D-fructose), confirmed that the interaction between PEG and the sulfamate moiety is essential for the formation of the new polymorphic form.

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