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Solid state NMR perspective of drug–polymer solid solutions: a model system based on poly(ethylene oxide)

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Abstract

Poly(ethylene oxide) (PEO) was tested as a polymer matrix for solid dispersion to enhance drug bioavailability. Solid state nuclear magnetic resonance (NMR), X-ray diffraction (XRD), and transmission electron microscopy (TEM) were utilized to characterize the high miscibility between PEO and ketoprofen, a model for crystalline drugs with poor water solubility. The experimental data demonstrated that ketoprofen in the melt-processed blend formed a complete molecular dispersion within the amorphous domain of PEO, resulting in high molecular mobility of ketoprofen in the melt-processed blend that leads to enhanced dissolution rate of ketoprofen in aqueous media. Hydrogen bonds between the carboxylic group of ketoprofen and the ether oxygen of PEO, as detected by solid-state NMR, are the likely source for the high miscibility between ketoprofen and PEO. Such drug/polymer molecular interactions promote dispersion of ketoprofen into amorphous phase of PEO at temperatures well below melting points of both crystalline ketoprofen and PEO. Consequently, melt-processing temperatures can be reduced significantly to avoid thermal degradation. The processing conditions can be also flexible while maintaining reproducibility of the physico-chemical properties of the blend. Furthermore, the high degree of drug/polymer molecular interactions stabilizes the morphology of the blend during storage.

Keywords: Poly(ethylene oxide); Solid state NMR; Solid dispersion; Solid state characterization; Bioavailability; Melt extrusion

1. Introduction

The large number of drugs characterized by low oral bioavailability has resulted in a continued focus of research activities in the area of increasing drug absorption (Ford, 1986; Serajuddin, 1999; Broman et al., 2001). Often times the limitation in bioavailability lies in poor solubility or low dissolution rate; therefore formulation approaches that can address these issues will result in an increased bioavailability (Ford, 1986; Serajuddin, 1999). One such approach that holds much promise is solid dispersion formulation, particularly those dispersions prepared from melt-processed methods due to their simplicity (Broman et al., 2001; Schacter et al., 2003). The challenge in applying this approach is to select a polymer system with a relatively low melting point and a high compatibility for the drug in order to process at low temperatures and yield stable dispersions with reproducible physico-chemical properties.

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Poly(ethylene oxide) (PEO) is a crystalline, non-ionic, hydrophilic polymer family commonly used in pharmaceutical controlled release applications (The Dow Chemical Company, 2002). Although the chemical structure of its repeat unit is identical to that of polyethylene glycol (PEG), the PEO family is distinguished by significantly higher molecular weights relative to PEG. Specifically, the molecular weight of PEO ranges between 100,000 and 7 million daltons. Similar to semi-crystalline PEG polymers, a relatively low melting point (68 °C) of PEO has generated heightened interest in the use of PEO in melt extrusion applications (Zhang and McGinity, 1999).

Thermal analysis data were obtained previously from heating tablets prepared from blends of 80% of PEO and 20% of an active agent, including ketoprofen, ibuprofen, sulfathiazole, hydroflumethazide, and tolbutamide (Schacter et al., 2003). Although each individual active compound was decidedly crystalline as demonstrated by its strong melting endotherm observed in the thermograms of the neat compound, consistently the corresponding endotherms were conspicuously absent in the thermograms of the blends. These DSC results suggested that the active agent is dissolved into the PEO melt during heating of the compressed powder blend. Similar miscibility behavior of PEO with flurbiprofen was also noted by Ozeki et al. who attributed it to the precedent melting of PEO that increased the mobility of the polymer chains and thereby its interactions with the drug (Ozeki et al., 1997). Such interactions can dramatically facilitate the solid dispersion formulation by reducing processing temperatures, increasing flexibility of processing parameters, and enhancing the thermodynamic stability of the formulated dispersion. In this work, solid state NMR, XRD, and TEM are used extensively to characterize the nature of the polymer–drug interactions between PEO and ketoprofen, a model for poorly water-soluble active compound (Fig. 1). In particular, solid state NMR was utilized to probe drug/polymer interactions in terms of both molecular structure and dynamics (Fyfe, 1984; Schmidt-Rohr and Spiess, 1994). Such detailed information of drug/polymer interactions on the molecular level is not readily available from the traditional analytical techniques used to study drug/polymer blends, such as XRD, IR, and thermal analysis. As demonstrated in this work, both molecular structure and dynamics of the drug and the polymer matrix are related directly to bioavailability of the drug/polymer blend.

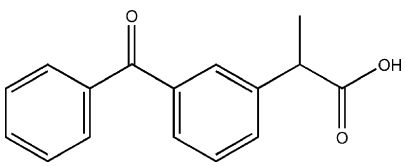

Fig. 1. Chemical structure of ketoprofen. Melting point of ketoprofen is 94 °C.

2. Materials and method

2.1. Tablets of non-melt-processed blend

Poly(ethylene oxide) with approximate molecular weight of 100,000 Da was obtained from The Dow Chemical Company. Ketoprofen was purchased from Sigma-Aldrich. Using methanol as an internal quantitation standard, the ^{1}H solution NMR of ketoprofen in deuterated methylene chloride indicated that the active compound is over 99% pure and therefore was used as received (Kasler, 1973). Tablets containing a blend of drug and PEO were prepared by mixing 80 g of PEO (screened through a 20 mesh screen) and 20 g of drug with a planetary mixer at 30 rpm for 90 s. The powder mixture weighted as 450 mg was placed in a die for compression using a hand operated Carver press. The powder was pressed at 1333 psi for 10 s. Final tablet dimensions were 3.4 mm in thickness and 13 mm in diameter.

2.2. Tablets of melt-processed blend

A physical blend mixture was prepared by mixing 80 g of PEO (approximate molecular weight of 100,000 Da, screened through a 20 mesh screen) and 20 g of drug. For testing effects of additives to the drug dissolution rate of the durg/polymer blend, desired amount (1–3%) of crospovidone (Aldrich) or sodium dodecyl sulfate (SDS, purchased from Aldrich) was also added to the physical mixture in some cases. The physical mixture was wet granulated with 10% (w/w) distilled water in a planetary mixer for 3 min. The wet granulation was added to a Brabender Plasticorder with twin mixing heads at 20 rpm and the bowl tem-

perature set at 100 °C. The mixing speed was raised to 25 rpm for another 2–3 min after addition. Water was used as a temporary plasticizer for lubricating the granulate as it is processed in the Plasticorder, but it is eliminated during the processing at 100 °C, as indicated by ^{1}H solution NMR of the melt-processed blend. The material was then spooned out and placed in a stainless steel die (6.35 cm × 6.35 cm × 0.8 cm) with aluminum liners on either side. The die with polymer mixture was placed between heated platens (100 °C) and allowed 1 min of heat without pressure followed by 1 min of melt pressing at 2000 psi. The pressure was then lowered to 1000 psi and the heater was shut off. The die containing the polymer mixture was allowed to remain between the platens until reaching room temperature. Tablets were punched out of the non-tacky and stiff plaque using a cork borer. The punched tablets were 3.4 mm in thickness, 13 mm in diameter and 450 mg in weight.

No thermal degradation was detected in the melt-processed tablets using ^{1}H and ^{13}C solution NMR. Specifically, the melt-processed blend was dissolved in deuterated methylene chloride for solution NMR analysis using a Varian/Chemagnetics Infity-500 NMR spectrometer with ^{1}H and ^{13}C resonance frequencies at 500.19 and 125.785 MHz, respectively. No extra peaks due to thermal degradation of ketoprofen or PEO were detected. In addition, PEO was investigated for possible reduction of molecular weights due to thermal degradation in the same NMR experiments. No significant increase in the peak areas due to the hydroxyl end groups of the polymer chain was observed, which is consistent with an earlier work that indicated that PEO at this relatively low molecular weight undergoes little to no degradation during melt extrusion at 100 °C (Huang et al., 2000).

2.3. Transmission electron microscopy (TEM)

Samples were cryo-microtomed (faced) at −75 °C (Reichert, Leica, Ultracut E with FC4 cryo-station), while they were protected from moist air in a chamber during all operations. When samples returned to room temperature they were stained (exposed to) with ruthenium tetra-oxide vapor from 0.5% aqueous solution for 25 min. Samples were then inspected with a TEM (Hitachi 500) ($t = 10$ nm) at 100 kV.

2.4. X-ray powder diffraction (XRD scans)

Powder X-ray diffraction patterns were obtained using a custom built hyphenated DSC-XRD (40 kV and 30 mA) instrument equipped with a copper ($d = 1.54599$ Å) tube X-ray source, a primary beam germanium monochromator, and a linear position sensitive detector with an angular resolution of 0.02°. The XRD data were analyzed using the software package JADE 6.0 (MDI, Livermore, CA).

2.5. Dissolution of ketoprofen

In vitro dissolution studies on non-melt-processed and melt-processed tablets containing 90 mg of ketoprofen were performed using the Vankel (Total Solution) paddle apparatus. The dissolution medium was 1000 ml of 1 N HCl at 37 ± 0.5 °C and stirring rate was 100 rpm. The six sample vessels were sampled at six different time intervals using an auto-sampler. Concentrations of the dissolved ketoprofen were determined using the Carey 50 spectrophotometer with the wavelength set between 258 and 260 nm.

2.6. Stability studies

Samples were placed in loosely covered glass dishes and stored for one month in a chamber that provided an environment of 40 ± 0.5 °C and 75% ± 2% RH. For comparison with samples stored at ambient condition, some samples were stored in a polyethylene bag at room temperature and placed in a lab drawer for one month before analysis.

2.7. Solid state NMR analysis

The ^{13}C single-pulse direct-polarization (or Bloch-decay) magic angle spinning (SP/MAS) experiments were used to study changes of molecular structures in the drug/PEO blends. To obtain quantitative distributions of different functionalities in the sample using the SP/MAS experiments, ^{13}C spin-lattice relaxation time (T_1) was estimated using the saturation-recovery technique. To monitor changes in molecular mobility, the cross-polarization magic angle spinning (CP/MAS) experiment was used to selectively detect rigid components in samples. The line shape of a ^{1}H solid-state NMR spectrum is very sen-

sitive to molecular motion, and variable-temperature high-speed magic angle spinning ^{1}H solid state NMR was thus used to monitor phase transition of the drug/PEO blends.

All of the solid state NMR experiments were conducted on a Varian/Chemagnetics CMX-360 spectrometer using a Doty XC5 5 mm double resonance MAS probe with ^{1}H and ^{13}C resonance frequencies at 360.240 and 90.598 MHz, respectively. Neat ketoprofen powder samples were packed directly in a ceramic MAS rotor (the sample holder for solid state NMR measurements). Tablets of the non-melt-processed blends as well as melt-processed blend samples were cut into small pieces before they were packed into the rotor. The magic angle spinning rates were set at 10 kHz. High power proton decoupling (63 kHz) was employed during the detection period for both ^{13}C SP/MAS and CP/MAS experiments. The actual temperature of the sample was calibrated using ^{207}Pb NMR of $Pb(NO_3)_2$.

3. Results and discussion

3.1. Variable temperature XRD study of ketoprofen-PEO non-melt-processed blend

The highly crystalline nature of PEO results in a clearly resolved and intense XRD pattern (Fig. 2). The positions of the XRD peaks associated with crystalline ketoprofen that are sufficiently distinguished from the PEO peaks appear at 2θ angles of 6.5°, 13.5°, 17.5°, 24°, and 29.5°. The ketoprofen/PEO non-melt blend was analyzed using the DSC-XRD instrument with 1 °C increments per scan ($12° < 2\theta < 28°$). This temperature ramping rate was selected in order for the kinetics of morphological change to "keep up" with the temperature ramp, thus allowing any morphological changes that occur at a given temperature to complete before the temperature is further increased. When the temperature reached 51 °C, the peaks unique to ketoprofen at the 2θ angles of 13.4°, 17.5° and 24° lost resolution, though the PEO peaks were still well defined. Although previous works on solid-dispersions based on PEO or PEG proved that an active drug can dissolve into melts of crystalline PEO or PEG at or slightly above their crystalline melting temperatures (Ozeki et al., 1997; Jachowicz et al., 2000), our variable-temperature XRD data indicate that ketoprofen dissolves into the amorphous fraction of solid PEO even before the crystalline PEO melts, while the polymer is still technically a solid. The nature of such solid–solid interaction at the molecular level will be further revealed later in this paper using variable-temperature solid-state NMR techniques.

In order to test flexibility of the process parameters necessary for dispersing ketoprofen in PEO, phys-

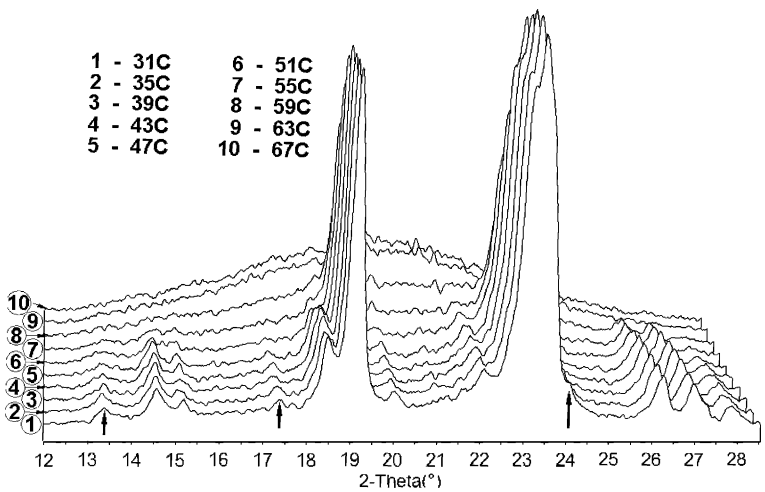

Fig. 2. Variable temperature XRD ($12° \leq 2\theta \leq 28°$) of non-melt-processed blend as temperature is increased. Vertical arrows point to unique ketoprofen peaks in this range.

ical mixtures of PEO and ketoprofen were prepared, heated to 100 °C and cooled under one of the three cooling conditions: (1) at a controlled rate of 1 °C/min, (2) cooled in a water bath at a constant temperature of 15 °C while kept in a waterproof bag, (3) quenched in liquid nitrogen. In all of the three cooling tests, PEO re-crystallized as observed by re-emergence of the characteristic XRD peaks from the crystalline PEO. As expected, a higher cooling rate leads to formation of smaller crystallites of PEO, resulting in broader XRD peaks as shown in Fig. 3. However, despite radically different cooling rates used in the tests, ketoprofen remained amorphous after all three cooling tests, as indicated by the absence of the XRD pattern of ketoprofen (Fig. 3). Ketoprofen, therefore, once dispersed within the polymer matrix remains irreversibly dispersed even while PEO re-crystallizes during cooling to room temperature. This is a clear demonstration of the relative ease in forming solid dispersions of a drug using PEO as the polymer matrix. Moreover, the result suggests that the thermodynamic drive to form the drug dispersion in a PEO solid solution is sufficiently strong that the process window can be wide without compromising reproducibility of physico-chemical properties. Scaling up such a system is thus facilitated since uniform process conditions throughout the bulk of the mixture are not necessary for achieving a complete molecular dispersion of the drug.

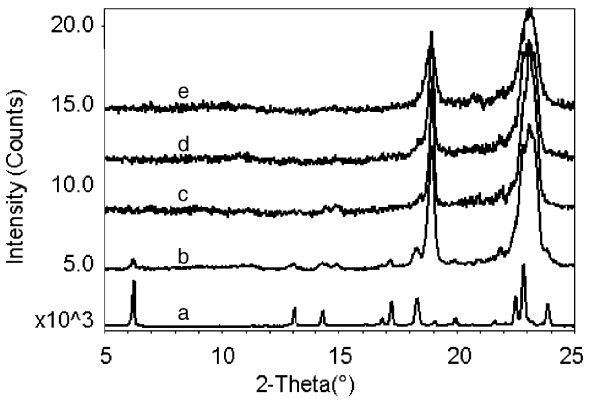

Fig. 3. XRD ($5° \leq 2\theta \leq 25°$) of (a) ketoprofen powder; (b) non-melt-processed blend; (c) melt-processed blend cooled at 1 °C/min; (d) melt-processed blend cooled in 15 °C water; (e) melt-processed blend quenched in liquid nitrogen.

3.2. TEM analysis of PEO/ketoprofen melt-processed blends

Initially, scanning electron microscopy (SEM) was used to inspect the morphology of ketoprofen/PEO solid dispersions. However, at the resolution of SEM, no distinguishing morphological characteristics were visible. Consequently, samples were analyzed with TEM (Fig. 4). The ruthenium oxide staining technique described by Trent et al. was used in order to distinguish between the crystalline and amorphous phases of the polymer (Trent et al., 1983). As described by Trent et al., the diffusion of the RuO_4 vapor is expected to occur more readily in the amorphous phase relative to the crystalline region and therefore darker stained lines in Fig. 4 are most likely due to the amorphous phase between crystallites. Using this method, it was possible to distinguish the crystalline and amorphous domains of PEO in both the neat melt-processed PEO and the ketoprofen/PEO melt-processed blend. Although the morphology of the two types of samples resembled each other, the amorphous regions of PEO that lie between the crystalline regions were wider in the blend samples relative to neat PEO. This suggests that the ketoprofen in the dispersion resides in the amorphous region. The presence of the crystalline phase in PEO most likely assists in the stabilization of the morphology since it can function as a barrier to diffusion within the matrix.

3.3. ^{13}C SP/MAS solid state NMR

The ^{13}C SP/MAS NMR spectrum of the neat ketoprofen powder was compared with those of ketoprofen in both the non-melt- and melt-processed PEO blends (Fig. 5). The ^{13}C NMR peak assignments are summarized in Table 1. The carboxyl chemical shift of 184.3 ppm in the pure crystalline ketoprofen indicates that the carboxylic acid groups are in almost deprotonated form within a strong intermolecular hydrogen bonding network (Gu et al., 1994), which is consistent with the crystalline structure of ketoprofen determined by X-ray single crystal diffraction (Briard, 1990). However, the carboxyl chemical shift of ketoprofen in the melt-processed blend is reduced by as much as 7.8 to 176.5 ppm. Since the strong intermolecular hydrogen bonds among carboxyl groups stabilize the crystalline structure of ketoprofen, the observed large

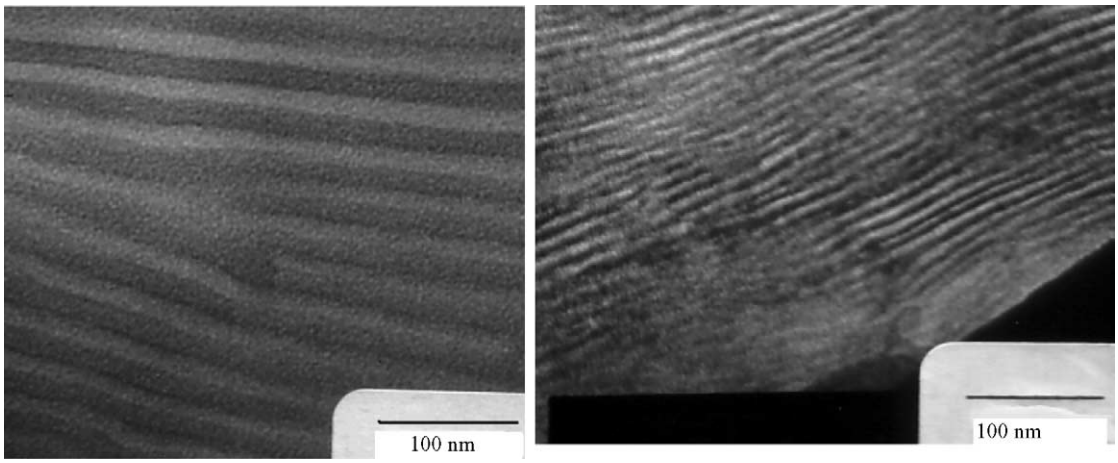

Fig. 4. TEM micrographs of melt-processed neat PEO (right) and melt-processed blend (left).

change of the carboxyl chemical shift indicates that the original ketoprofen crystalline structure has been altered significantly due to interactions between PEO and ketoprofen in the melt-processed blend. Specifically, the original strong hydrogen bonds present within the neat crystalline ketoprofen are no longer detected in the melt-processed blend. The change in hydrogen bonding also results in an upfield shift of the CH peak, downfield shift of the ketone carbonyl chemical shift, and changes in the aromatic region of the spectra of the melt-processed blend compared with the neat crystalline ketoprofen. In the ^{13}C SP/MAS NMR spectrum of the melt-processed blend, complete absence of the characteristic ^{13}C NMR peaks from the neat crystalline ketoprofen indicates that a complete molecular dispersion of ketoprofen is achieved from the melting process.

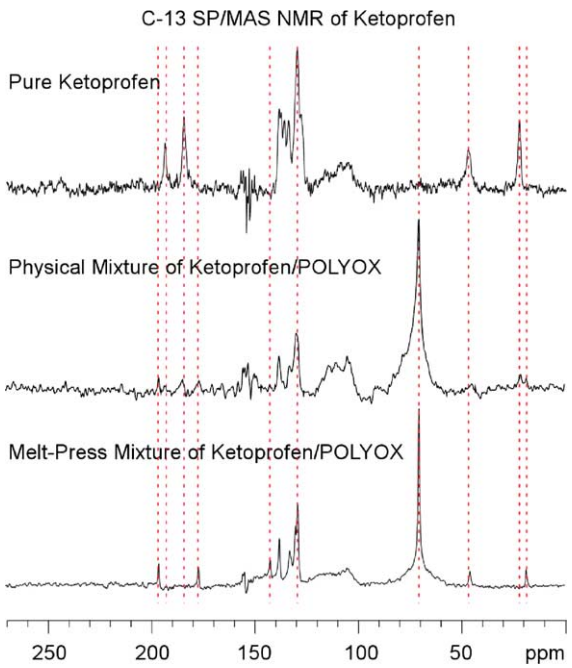

Fig. 5. ^{13}C SP/MAS NMR spectra of ketoprofen powder (top), non-melt-processed physical blend (middle), and melt-processed blend (bottom), acquired at 43 °C. Broad peaks between 100 and 125 ppm are due to the NMR probe background. Signals around 153 ppm are due to the central glitch.

Although the sample temperature during the ^{13}C NMR analysis was only 43 °C, surprisingly

Table 1
Summary of ^{13}C solid state NMR signal assignments

Chemical shift (ppm)	^{13}C NMR assignments
195.8	Ketone carbonyl carbon in the ketoprofen/PEO blends
193.4	Ketone carbonyl carbon in pure ketoprofen
184.3	Carboxylic acid carbon in pure ketoprofen
176.5	Carboxylic acid carbon in the ketoprofen/PEO blends
120–140	Aromatics in ketoprofen
70.2	CH_2 in PEO
46.6	CH in pure ketoprofen
45.5	CH in the ketoprofen/PEO blends
22.0	CH_3 in pure ketoprofen
18.5	CH_3 in the ketoprofen/PEO blends

the changes of the chemical shifts were also apparent in the ^{13}C SP/MAS NMR spectrum of the non-melt-processed blend of PEO and ketoprofen (Fig. 5). The spectrum of the non-melt-processed mixture displayed NMR peaks corresponding to both neat crystalline ketoprofen and ketoprofen dispersed in the melt-processed blend, indicating that the non-melt-processed physical mixture contains both crystalline ketoprofen and amorphous ketoprofen dispersed in PEO. The solid state NMR results suggested that intermolecular interactions between ketoprofen and PEO are present even in the non-melt-processed blend at temperatures as low as 43 °C. And the ketoprofen/PEO interactions in solid state start to disrupt the original ketoprofen intermolecular hydrogen bonds in the crystalline structure at temperatures markedly below the melting points of either PEO or ketoprofen, likely through the ketoprofen/PEO interface.

It is interesting to compare the ^{13}C solid state NMR spectra (Fig. 5) with ^{13}C liquid NMR spectra of the same set of samples in methylene chloride solutions (Fig. 6). Similar to what was observed in solid state NMR, the chemical shift of the carboxyl groups in the solution of the neat ketoprofen is 180.5 ppm, suggesting that intermolecular hydrogen bonds between carboxyl groups of ketoprofen still exist. Similarly, the chemical shift of the carboxyl groups in solution of the ketoprofen/PEO blends is reduced by 3.2 to 177.3 ppm. The NMR data suggest that the intermolecular hydrogen bonds among ketoprofen are replaced by the intermolecular hydrogen bonds between the carboxyl group of ketoprofen and the ether oxygen of PEO in the ketoprofen/PEO blends. The similarity between solid state NMR of the melt-processed blend and the solution NMR of the blends further confirms that a complete molecular dispersion of ketoprofen in PEO is formed in the melt-processed blend in the solid state. It is also interesting to note that there is no significant difference in the solution NMR spectra between non-melt-processed blend and melt-processed blend, as the same complete molecular dispersions are formed in the methylene chloride solutions irrespective of the original solid state morphology of the blends. In contrast, the solid state NMR indicates that the non-melt-processed blend contains both crystalline ketoprofen and molecular dispersion of ketoprofen in PEO, while the ketoprofen in the melt-processed blend is completely dispersed in PEO at the molecular level.

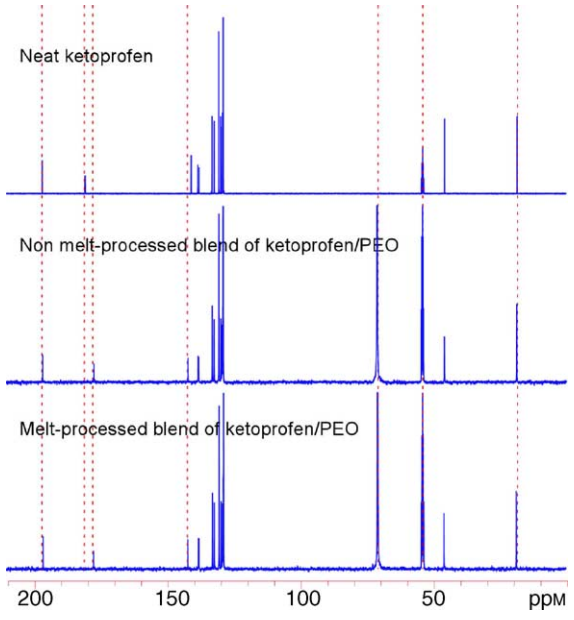

Fig. 6. ^{13}C solution NMR of pure ketoprofen (top), non-melt-processed physical blend (middle), and melt-processed blend (bottom), acquired at 20 °C. Continuous proton decoupling at 500.19 MHz with 3.3 s recycle delay was used to acquire the ^{13}C solution NMR spectra at 125.785 MHz. The peak at 53.8 ppm is due to the solvent CD_2Cl_2. To display the relatively weak signals from ketoprofen compared with PEO in the blends, the NMR spectra of the blends (middle and bottom) are vertically expanded, resulting the PEO peak at 70.75 ppm off the vertical scale in the figure.

The solid state NMR results have demonstrated the unique advantage of solid state NMR for analyses of complex drug/polymer dispersions compared with XRD and other traditional analytical techniques. The value of the solid-state NMR method lies in its capability for detecting, differentiating, and quantifying both crystalline and amorphous components in a complex mixture.

Furthermore, the particular sharp peaks observed in the ^{13}C SP/MAS NMR spectra of the melt-processed blend is illustrative of increased mobility of ketoprofen in the blend relative to its neat crystalline structure. The PEO peak at 70.2 ppm is also sharper in the NMR spectrum of the melt-processed blend relative to that of the non-melt-processed blend, suggesting, too, that PEO is more mobile when melt processed with keto-

profen. Therefore, the drug has a plasticizing effect on the polymer, likely due to interference of recrystallization of PEO from the presence of ketoprofen in the blend during the final cooling process.

3.4. ^{13}C CP/MAS solid state NMR

To monitor changes in molecular mobility in the blends, the ^{13}C CP/MAS technique was used to selectively detect rigid components in the samples with the ^{1}H to ^{13}C cross-polarization contact time of 2 ms (Fig. 7). Very weak methyl, carboxylic and ketone carbonyl carbon peaks were observed in the ketoprofen non-melt-processed blend, indicating an increased mobility of the ketoprofen molecules even without melt processing with PEO. In the melt-processed blend, only weak aromatic peaks from ketoprofen were detected, suggesting that ketoprofen in the melt blend is even more mobile than in the non-melt-processed blend.

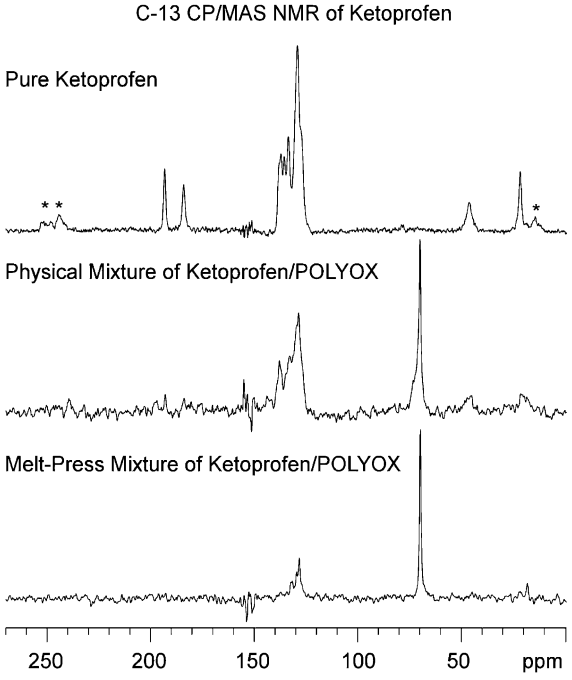

Fig. 7. ^{13}C CP/MAS NMR spectra of ketoprofen powder (top), non-melt-processed blend (middle) and melt-processed blend (bottom), acquired at 43 °C. Signals around 153 ppm are due to the central glitch. The peaks marked by "∗" are spinning side bands.

3.5. ^{1}H SP/MAS solid state NMR

The line shape of a ^{1}H solid-state NMR spectrum is very sensitive to molecular motion, as rotational molecular motion can effectively reduce the proton–proton nuclear spin dipolar couplings that dominate the ^{1}H solid-state NMR line shape. A decrease in the linewidth is indicative of increased molecular motion. The observed decrease of line width in the ^{1}H SP/MAS spectra of ketoprofen samples provided direct evidence for increase of molecular mobility in the ketoprofen/PEO blends (Fig. 8). Even in the non-melt-processed blend, the molecular mobility of ketoprofen has increased significantly, compared with ketoprofen in its neat crystalline form. The results suggest that ketoprofen can interact with PEO in the solid state at temperatures significantly lower than the melting point of either component, as indicated also from our ^{13}C NMR and XRD studies. On the basis of differences of ^{1}H NMR linewidths shown in the insets of Fig. 8, the molecular mobility of both ketoprofen and PEO in the melt-processed blend

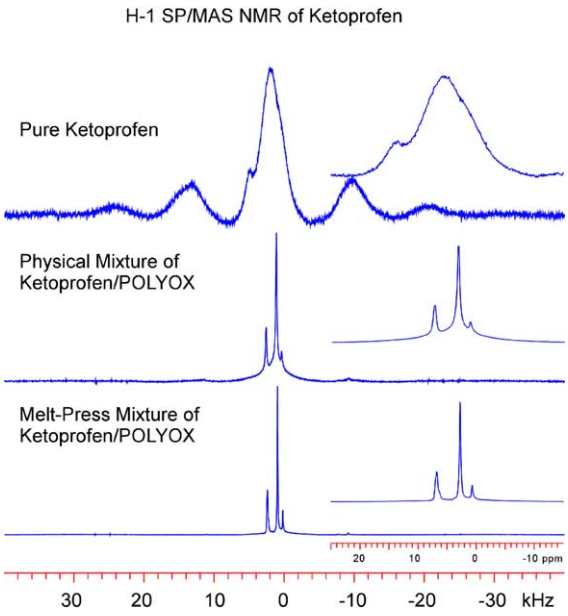

Fig. 8. ^{1}H SP/MAS NMR spectra of ketoprofen powder (top), non-melt-processed blend (middle) and melt-processed blend (bottom), acquired at 43 °C. In order to show details of the NMR signals from ketoprofen, insets of the NMR spectra between −15 and 25 ppm are also displayed.

is even higher than the one in the non-melt-processed blend.

3.6. Variable temperature ^1H SP/MAS solid state NMR

Variable-temperature ^{1}H SP/MAS technique was used to monitor changes of molecular mobility and phase transition of the physical blend with the temperature (Fig. 9). Significant line narrowing was observed at temperatures as low as 48 °C, indicating again that strong ketoprofen/PEO solid–solid interactions are present. A dramatic increase in molecular mobility is observed at 54 °C, the temperature onset for dissolution of ketoprofen into PEO, as suggested also from our previous XRD data. Line narrowing continued until the temperature reached 73 °C, the temperature at which PEO has completed its melting process. This gradual increase in ketoprofen mobility while still in the solid phase suggests that the ketoprofen crystal structure was steadily disrupted by the solid–solid interactions at the ketoprofen–PEO interface due to increase of mobility of the polymer chains in the amorphous PEO region. The high mobility of ketoprofen was retained even after cooling the blend to room temperature. The ^{1}H NMR linewidths and integration values of ketoprofen signals at 73 °C clearly show that ketoprofen molecules are completely dissolved in the PEO melt. Although above-mentioned microscopy, DSC, and XRD data suggest that ketoprofen can dissolve into PEO at temperatures well below the melting point of ketoprofen, the NMR results, in terms of ketoprofen mobility and intermolecular hydrogen bonds, provide evidence that the dissolution of ketoprofen molecules into PEO begins at even lower temperatures than the other data suggest. The NMR data also provided the direct proof that ketoprofen formed a complete molecular dispersion in PEO during the melt process.

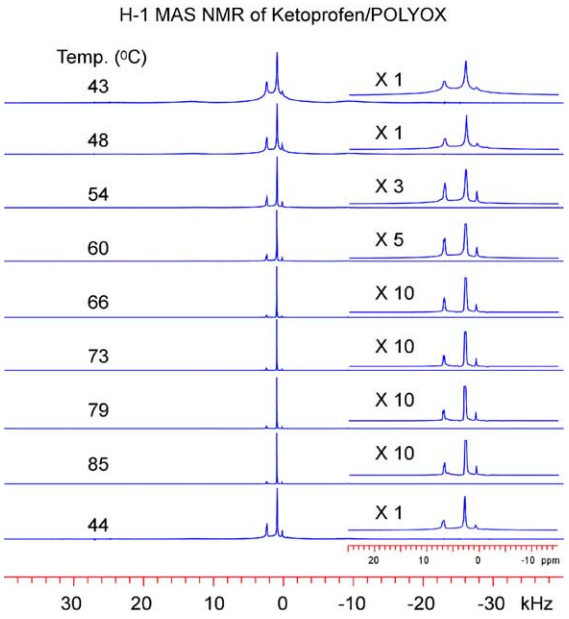

Fig. 9. ^{1}H SP/MAS NMR spectra of the physical blend of ketoprofen and PEO acquired with increasing temperatures, as marked on the spectra. The bottom spectrum was acquired after the blend cooled back to 44 °C. In order to show details of the NMR signals from ketoprofen, insets of the NMR spectra between −15 and 25 ppm are also displayed with vertical expansion factor shown by the side of the insets.

Combining solid-state NMR, XRD, and TEM results, a much better understanding of the drug dispersion process in PEO has been obtained at the molecular level. It is likely that intermolecular hydrogen bonds among ketoprofen molecules in the neat crystalline ketoprofen are replaced by weaker hydrogen bonds between the carboxyl group in ketoprofen and the ether oxygen of PEO when the two components are blended. The hydrogen bonds in the blend are most likely weaker than the ones in the neat ketoprofen, as indicated by higher mobility of ketoprofen in the blend relative to the neat crystalline ketoprofen. Consequently, the thermodynamic drive for the formation of the ketoprofen/PEO blend can be attributed mainly to the large increase in entropy as the blend is formed. Although weaker than the intermolecular hydrogen bonds in neat ketoprofen, the PEO/ketoprofen interactions are sufficiently strong to have a stabilization effect to prevent the re-crystallization of ketoprofen as the blend cools from the melt phase. The hydrogen bonds between ketoprofen and PEO also promote dispersion of ketoprofen into amorphous PEO at temperatures well below the melting points of crystalline ketoprofen and PEO. On the other hand, such weak ketoprofen/PEO hydrogen bonding and high ketoprofen molecular mobility in the melt-processed blend can increase significantly the dissolution rate of ketoprofen in aqueous media, as relatively high energy required to disrupt the crystalline structure of keto-

profen during the dissolution process is no longer needed.

3.7. Dissolution of ketoprofen

The dissolution rate of ketoprofen from the melt dispersions in PEO was tested and a comparison of the rate in the first 60 min was made to that of tablets of the non-melt-processed blend (Fig. 10). Equilibrium is established equally for the melt- and non-melt-processed blends and therefore the final concentrations in the media are the same for both types of the blends. However, the dissolution rate from the melt dispersion was 1.5 times the rate from the tablets of the non-melt blend of identical dimensions. The increased rate of dissolution can be attributed to the amorphous ketoprofen present in the solid dispersion relative to the crystalline ketoprofen present in the non-melt-processed blend. As indicated from solid state NMR, the difference in molecular mobility between the amorphous and crystalline phase of ketoprofen suggests that the energy required for dissolving ketoprofen in the molecular dispersion of PEO is significantly less than the energy required to dissolve crystalline ketoprofen. The increase of the drug dissolution rate in the melt-processed blend is thus directly related to its enhanced molecular mobility. However, the increase in the drug dissolution rate is tempered by the time necessary for the compact crystalline PEO phase to imbibe water, as demonstrated by the comparison of the drug dissolution rates from the tablets with and without addition of crospovidone. Although XRD data indicated that addition of crospovidone did not affect amorphous morphology of ketoprofen in the melt-processed PEO blend (data not shown), the crospovidone increases the rate of erosion of the PEO matrix and therefore correspondingly increases the drug dissolution rate to 1.7 times that of the non-melt-processed blend (Fig. 10). In contrast, tablets of the non-melt-processed blend with added crospovidone did not demonstrate any increase in drug dissolution rate, since the rate is still limited by dissolution of ketoprofen crystallites in the non-melt-processed blend. Addition of surfactants such as sodium dodecyl sulfate (SDS) can also increase drug dissolution rate of solid dispersions (Sjökvist et al., 1992). With 1% (w/w) SDS (Sigma-Aldrich) added to the melt process formula-

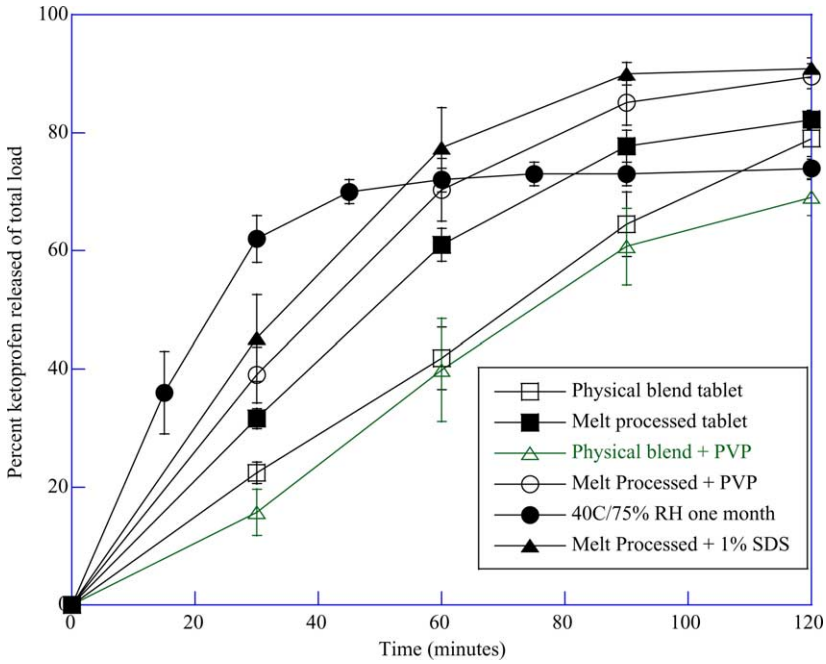

Fig. 10. Dissolution of ketoprofen at 37 °C in 1 N HCl.

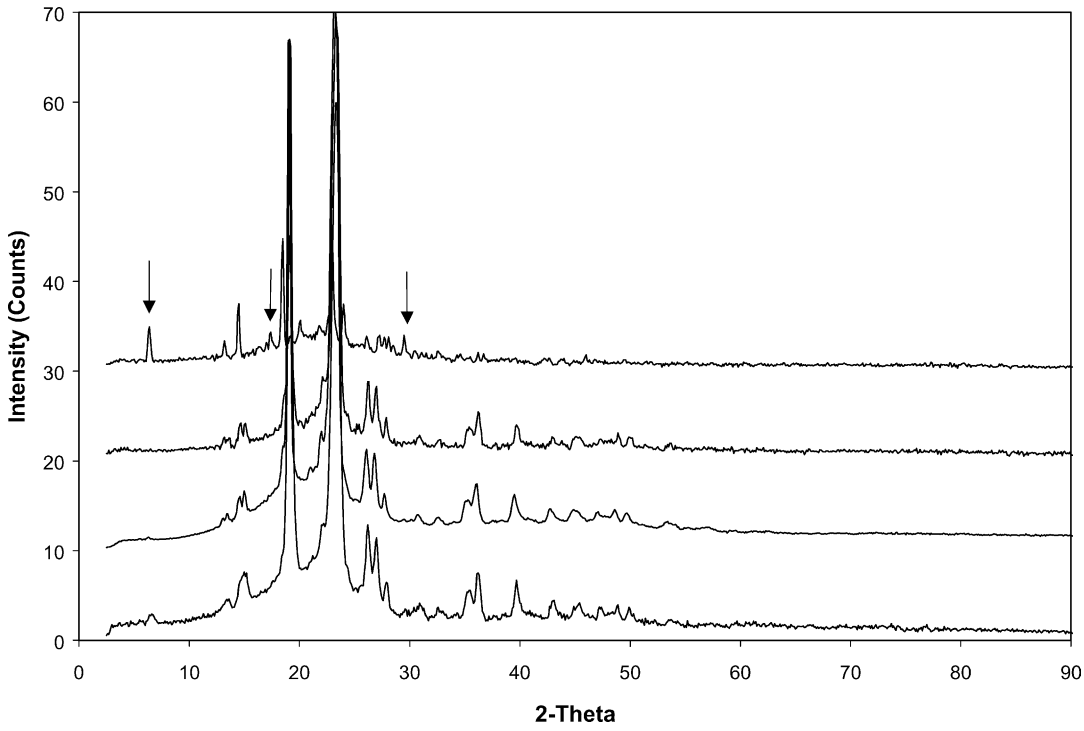

Fig. 11. XRD: (top) non-melt-processed ketoprofen; (2nd) non-melt-processed PEO; (3rd) freshly made melt-processed blend; (bottom) melt-processed blend after one month in glass dish at 40 °C/75% RH. Arrows indicate unique ketoprofen peaks.

tion, we observed doubling of the drug dissolution rate from the melt-processed blend in the first 60 min relative to the non-melt-processed blend (Fig. 10). As a control, 1% SDS was added to the non-melt-processed blend and no significant difference in dissolution rate was observed compared with the non-melt-processed blend without SDS. In fact, increases in dissolution rate for the non-melt-processed blend were observed only after 2% (w/w) of SDS or more was added to the blend (data not shown). These results suggest that SDS is more effective than crospovidone in promoting water and drug to diffuse in and out of the PEO polymer matrix, thereby enhancing dissolution rate of both ketoprofen and the PEO polymer matrix.

3.8. Stability of dispersion

Arguably, the "Achilles heel" of all melt dispersions is their lack of stability when stored under challenging environmental conditions. In order to test their stability under significantly formidable conditions, melt dispersions were stored for one month in loosely covered glass petri dishes in a chamber set at 40 °C/75% RH for one month and a parallel set was stored under ambient conditions for one month. Samples were subsequently analyzed by XRD (Fig. 11). No change in physical appearance or XRD diffraction patterns was detected from the samples stored under ambient conditions for one month. In contrast, the samples stored under 75% relative humidity at 40 °C were highly swollen and tacky when removed. The XRD analysis indicated emergence of a very weak peak at 6° region from the crystalline ketoprofen, but weaker diffraction peaks associated with ketoprofen such as the peak at 29.5° were not observed. The XRD result suggested that a trace amount of the dispersed ketoprofen re-crystallized under the aggressive storage conditions. The ketoprofen from the melt blends stored at higher temperature and humidity actually demonstrated an increase in initial dissolution rate relative to the freshly made samples (Fig. 10), at-

tributed most likely to the increased water content in the polymer matrix when stored under aggressive conditions. However, the rate leveled off faster at a lower final concentration of ketoprofen. The changes that occurred when stored under these conditions require more study, particularly solid state NMR to investigate changes in molecular interactions. Packaging protections should be considered to avoid these changes.

4. Conclusions

Using the ketoprofen/PEO blends as model systems, the solid state NMR, XRD and TEM data have indicated that a high degree of miscibility can develop between a hydrophilic polymer and a poorly water-soluble crystalline drug. The spectroscopic and microscopic data clearly showed that ketoprofen disperses into the amorphous domain of PEO on the molecular scale when melt processed with PEO, resulting in much higher mobility of ketoprofen molecules compared with ketoprofen in the crystalline structure. Such high molecular mobility is directly related to enhanced dissolution rate of the melt-processed drug/PEO blend. Formation of intermolecular hydrogen bond between the carboxyl group of ketoprofen and the ether oxygen of PEO most likely is the source for the high miscibility between ketoprofen and PEO in the blend. The ketoprofen/PEO interactions can be detected even in non-melt-processed blends at temperatures as low as 43 °C. Such low-temperature miscibility between ketoprofen and PEO greatly facilitates the melt process method, as high processing temperatures can be avoided and therefore the risk of thermal degradation of the drug is significantly reduced. Moreover, the processing parameters can be flexible, as uniform physico-chemical properties of the product can be maintained even if it is not possible to obtain uniform conditions throughout the melt process. Furthermore, once the melt-processed blend is formed, the intermolecular interactions can maintain stability of the morphology of the blend during storage. In this work, we have also demonstrated that the solid state NMR is a very powerful tool for characterizing molecular structure, molecular mobility, and solid morphology of complex drug/polymer blends.

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