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Characterization of Poly(Ethylene Oxide) as a Drug Carrier in Hot-Melt Extrusion

Lei Li, Omar AbuBaker* and Zezhi J. Shao
Pfizer Global Research and Development, 2800 Plymouth Rd., Ann Arbor, MI 48105, USA

ABSTRACT Poly(ethylene oxide) (PEO) as a drug carrier in hot-melt extrusion was studied by using a model drug, nifedipine, in a twin-screw extruder. Binary mixtures of PEO and nifedipine have been shown to be amenable to hot-melting at a temperature as low as 70°C, well below nifedipine's melting point (172°C). Hot-stage microscopy provided visual evidence that nifedipine can form a miscible dispersion with PEO at 120°C. Complete loss of nifedipine crystallinity when extrudated at and above 120°C with a drug loading of 20% (w/w) was further confirmed by differential scanning calorimetry (DSC) and X-ray diffraction. Cross-sectional imaging of the extrudates using scanning electron microscopy indicated homogeneous drug distribution inside PEO when the processing temperature was above 120°C. Raman spectroscopy confirmed drug-PEO interactions at a molecular level. Cryo-milled extrudates showed significant improvement in dissolution rate compared to either pure nifedipine or the physical mixture of PEO and nifedipine. A state of supersaturation was achieved after 10-minute release in pH 6.8 phosphate buffer. Finally, stability study demonstrated that the solid dispersion system is chemically stable for at least 3 months under the conditions of both 25°C/60% RH and 40°C/75% RH. Overall, PEO appears to be a promising aid/carrier to solublize poorly soluble drugs through the formation of solid dispersion via hot-melt extrusion, thereby improving dissolution and absorption.

KEYWORDS Hot-melt extrusion, Poly(ethylene oxide), Nifedipine, Solid dispersion, Dissolution

INTRODUCTION

It has been estimated that more than 40% of newly discovered compounds and marketed drugs are either poorly soluble or water insoluble (Dubin, 2005). Developing platforms to enhance drug solubility and ultimately increase in vivo bioavailability has become imperative. A solid dispersion system is one such platform (Serajuddin, 1999) and has become one of the most actively pursued areas after Sekiguchi and Obi (1961) first demonstrated that the eutectic mixtures of sulfathiazole and urea exhibited faster dissolution and better absorption upon administration.

Solid dispersions can be formed through either the solvent method or melting/fusion. In the former, drug and carrier are both dissolved in a

*Current address:
Omar Abu Baker, GlaxoSmithKline, 709 Swedeland Rd., UW2913, PO Box 1539, King of Prussia, PA 19406,
E-mail: omar.a.abu-baker@GSK.com

Address correspondence to Lei Li, Biopharmaceutics Research and Development, Bristol-Myers Squibb, One Squibb Dr., New Brunswick, NJ 08903, USA; Tel: 732-227-6698; Fax: 732-277-3818;
E-mail: Lei.Li@bms.com

common solvent, and then the system is allowed to solidify upon evaporation of the solvent. Melting/fusion involves melting a drug and carrier at elevated temperatures followed by solidification after cooling. Continuous processing utilizing hot-melt extrusion has made this method more appealing (Doherty & York, 1987). Drug molecules in a solid dispersion are often in the state of amorphous embedded in crystalline, glass carrier or solutes in a carrier solution, or a mixture thereof (Breitenbach & Magerlein, 2003), resulting in solubility and dissolution enahancement (Grunhagen, 1996; Hulsmann et al., 2000). Formation of most solid dispersions requires elevated temperature very close to or above the drug melting point (Crowley et al., 2004; Schachter et al., 2004), which could result in polymer thermal degradation (Crowley et al., 2002) and drug oxidation/decomposition (Chiou & Riegelman, 1971). Hence, selection of a drug carrier that interacts with the drug or the addition of a plastisizer is preferred in order to lower the processing temperature.

Poly(ethylene oxide) (PEO), a crystalline non-ionic hydrophilic polymer, has been studied previously for holt-melting applications by using ketoprofen, ibuprofen, flurbiprofen, sulfathiazole, hydroflumethazide, and tolbutamide (Ozeki et al., 1997; Schachter et al., 2003). Absence of the DSC endotherms has been attributed to the dissolution of the drugs into the PEO melt during heating of the drug-PEO blends. Solid-state nuclear magnetic resonance, X-ray diffraction (XRD), and transmission electron microscopy (TEM) further confirmed ketoprofen being dispersed within the amorphous domain of PEO, likely through hydrogen bonding between the carboxylic group of ketoprofen and the ether oxygen of PEO (Schachter et al., 2004). In this work, we selected nifedipine as a model drug for holt-melt application and characterized the dispersion by using DSC, XRD, scanning electron microscopy (SEM), and Raman microscopy. Additionally, dissolution and stability have been performed and compared with that of the physical mixture.

MATERIALS AND METHODS

Chemicals

Poly(ethylene oxide) (POLYOX® WSR N-80) with approximate molecular weight of 200,000 Da was obtained from Dow Chemical Co. (Midland, MI, USA). Nifedipine was sourced internally from Pfizer Global Manufacturing. All other solvents, acids, and bases were obtained from VWR (West Chester, PA, USA); and all reagents and buffer salts were obtained from Sigma (St. Louis, MO, USA).

Hot-Melt Extrusion

PEO was blended with nifedipine at a weight ratio of 4:1 in a Turbular mixer for 5–10 minutes until homogeneously mixed. A bench top twin-screw extruder, DACA Microcompounder (DACA Instruments, Goleta, CA, USA), was used to perform the hot-melt extrusion process at a screw rotation speed of 100 rpm after the temperature was set and stabilized (70°C–200°C). The powder material was manually fed from the hopper into the extruder, and the extrudate was pushed out of the orifice at the end of the screws. The extrudates were then cut into pieces for further characterization. A Spex CertiPrep 6800 freezer mill (Spex CertiPrep Inc., Metuchen, NJ, USA) was used to perform the cryogenic milling of the extrudates. The sample was first placed in a 190-mL vial, milled for 20 minutes, and then transferred into a 25-mL vial and milled for another 20 minutes.

DSC and XRD

A Q1000 DSC (TA Instruments, New Castle, DE) was used to perform thermal analysis of the drug, the polymer, their mixtures, and extrudates. Temperature ramp speed was 10°C/min from 25°C to 250°C with a nitrogen flow rate of 50 mL/min. The heat flow was measured during a temperature cycle.

X-ray diffraction patterns were generated by using a Bruker D8 General Area Detector Diffraction System (Bruker AXS Inc., Madison, WI, USA). The extrudates were thin-sliced along cross-section and placed on a sample holder for scanning from 5 to 40 degrees of 2-theta angle.

Hot-Stage Microscopy

A Leitz optical microscope equipped with a temperature-controlled Mettler-Toledo FP82HT hot-stage

was used to observe the crystal form change under temperature control with snapshots taken via a colored charged-couple device (CCD) camera throughout the process.

SEM Imaging

A Quanta 200XL environmental scanning electron microscope (FEI Co., Hillsboro, OR, USA) was used to observe drug distribution in extrudates. The sample was stuck on the stub with no coating applied. The chamber was operated at a low vacuum mode at 1 Torr with accelerated voltage of 5 kV.

Raman Microscopy

A HoloLab Series 500 Raman microscope (Kaiser Optical System, Inc., Ann Arbor, MI, USA) was used to obtain Raman spectra of the extrudates with resolution of 4 cm^{-1}. The laser power was set at 5 mW because of the potential nifedipine degradation. The spot size was about 20 μm with a 50 × lens. At least three spectra were taken for each sample. Grams32/AI version 6.00 spectral data processing software (Thermo Elecrton Co., Waltham, MA, USA) was used to process the spectra.

Stability Studies

Samples were placed in high-density polyethylene bottles, loosely covered, and stored in chambers prequilibrated to 25°C/60% RH and 40°C/75% RH for 1 and 3 months.

Approximately 7.5 mg of the extrudates was weighed out, and dissolved in 20 mL of 50:50 acetonitrile/H_2O, then diluted to 50 mL in the same media. Absorbance was measured at 236 nm using a UV spectrometer (USP-NF, 2005). Samples were run in triplicate.

Dissolution Testing

Milled extrudates were weighed out and placed into a 500-mL amber flask containing 500 mL of 0.05 M phosphate buffer of pH 6.8. The flask was stirred, sampled at different time intervals, filtered through a 0.45-mm filter, then diluted properly with acetonitrile, and absorbance measured by UV spectrometer. All experiments were performed under light control or in a dark room to prevent nifedipine from photodegradation. Samples were run in triplicate.

RESULTS AND DISCUSSION

Hot-Melt Extrusion of PEO with Nifedipine

The nifedipine-PEO mixture appears to be very amenable to hot-melt extrusion when processed at a temperature range of 70°C to 200°C. Even at 70°C, which is just slightly above the melting point of PEO (62°C) and yet far below the melting point of nifedipine (172°C), the extrusion process can be completed without any difficulty. Below 120°C, the extrudates appeared opaque and light yellowish, while at and above 120°C the extrudates became brightly yellow and transparent. By thermal gravimetric analysis (TGA) both PEO and nifedipine decomposition temperatures are well above 200°C (411°C and 287°C, respectively). The residence time of drug-polymer mixture in the extruder is typically less than 1 minute. Therefore, degradation of the PEO and nifedipine, if any, can be regarded as negligible in this process. The inherent thermoplasticity of PEO makes it an ideal choice for holt-melt process, as demonstrated herein.

DSC and XRD Characterization

The DSC thermograms for bulk polymer, pure nifedipine, nifedipine-PEO physical mixture, and extrudates processed at different temperatures are shown in Fig. 1. Melting point of bulk PEO is at ~62°C for this easy-to-crystallize polymer that has over 85% crystallinity. Pure crystalline nifedipine melts at ~172°C. Upon mixing with PEO, there was only a small nifedipine melting peak appearing and its heat of fusion was only 10% that of the pure crystalline drug, indicating PEO melt being a good solvent for nifedipine. The melted PEO started to dissolve the drug as its mobility increased. Ozeki et al. (1997) reported similar findings for flurbiprofen in PEO.

Upon extrusion with PEO, the drug-melting peak had essentially completely disappeared, indicating loss of crystallinity in the molten PEO. There also appeared to be a decrease in the PEO melting point after extrusion with nifedipine (62°C for pure PEO, for PEO/nifedipine physical mixture, and for extrudates of pure PEO processed at 70°C, but 59°C for extrudates of PEO with 20% of nifedipine processed

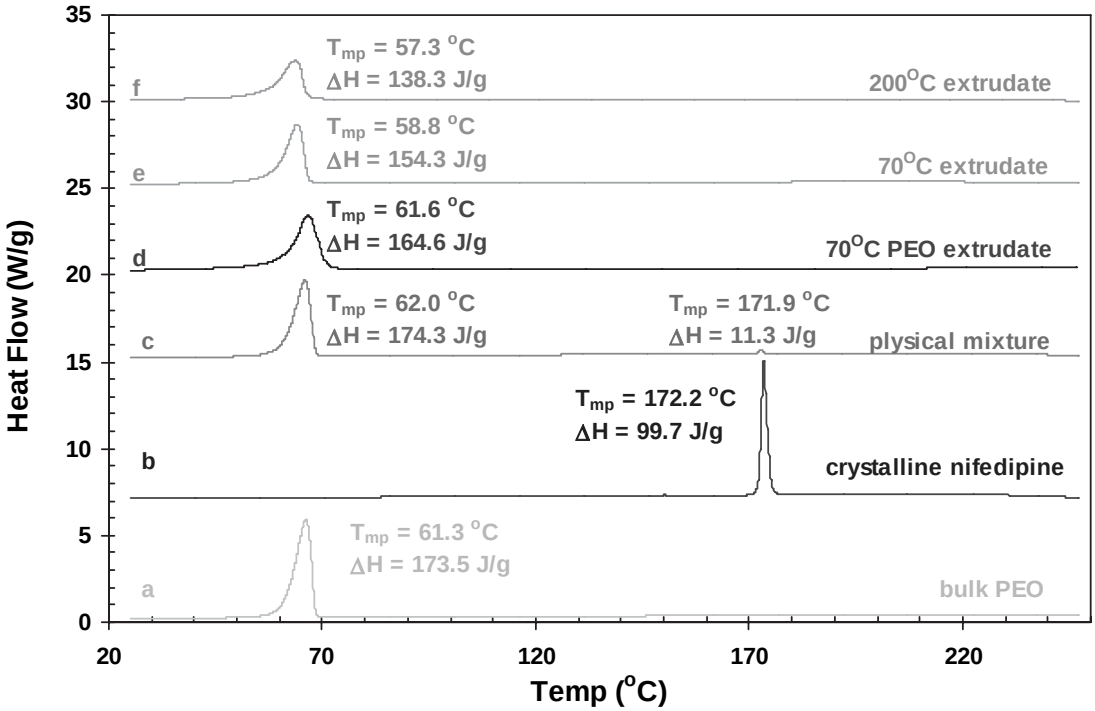

FIGURE 1 DSC of Bulk Nifedipine, its Physical Mixture with PEO, and Extrudates.

at 70°C, and 57°C for extrudates with same drug loading processed at 200°C), demonstrating molecular interactions between PEO and nifedipine. Such interactions resulted in a lower energy needed for phase transition in the extrudates compared to that of the pure PEO. Calculation of fusion heat (as shown in Fig. 1) indicated a gradual decrease as a result of the increase in extrusion temperature, demonstrating loss of PEO crystallinity.

XRD was then used to confirm loss of drug crystallinity and results are shown in Fig. 2. PEO has two dominant peaks at 2-theta angles of 19.3 and 23.4 degrees. Following extrusion, their intensity became much lower although was still present in the extrudates. Nifedipine has three peaks at 8.2, 10.5, and 12 degrees, which are clearly separated from the PEO's peaks. These peaks became much reduced following extrusion with PEO at 70°C. Drug crystallinity appeared to have been completely lost upon extrusion at 120°C.

Both DSC and XRD results, therefore, clearly demonstrated loss of nifedipine crystallinity when extruded at a temperature well below its melting point (172°C). This finding indicates that PEO melt can effectively dissolve this drug, forming a solid dispersion in the solid state.

Crystal Morphological Change

To further confirm our findings and assumptions, visualization of the crystal dissolution process of nifedipine in PEO at elevated temperature was performed by using a polarized microscope equipped with hot-stage, whereby morphological changes can be directly observed. Photomicrographs are shown in Fig. 3, after heating the 4:1 PEO:drug blend from room temperature to 200°C at a ramp-up rate of 10°C/min (same as in DSC experiments), then cooling down to room temperature. At the start of heating (Fig. 3a), needle-shaped nifedipine crystals were clearly visible while PEO appeared as dark-colored particulates. After the sample was heated to 70°C (slightly above the PEO melting point), PEO melting became apparent, forming round-shaped droplets, and needle-shaped nifedipine became surrounded by the PEO as shown in area II of Fig. 3b and started to melt, whereas crystalline nifedipine not in contact with melted PEO remained in the original shape and size (area I). At 130°C (Fig. 3c), nifedipine crystals covered by PEO have been mostly dissolved, but the nifedipine crystals not in touch with PEO remained the same. Melting of such isolated crystals only started upon heating to ~170°C (Fig. 3e). At 200°C all

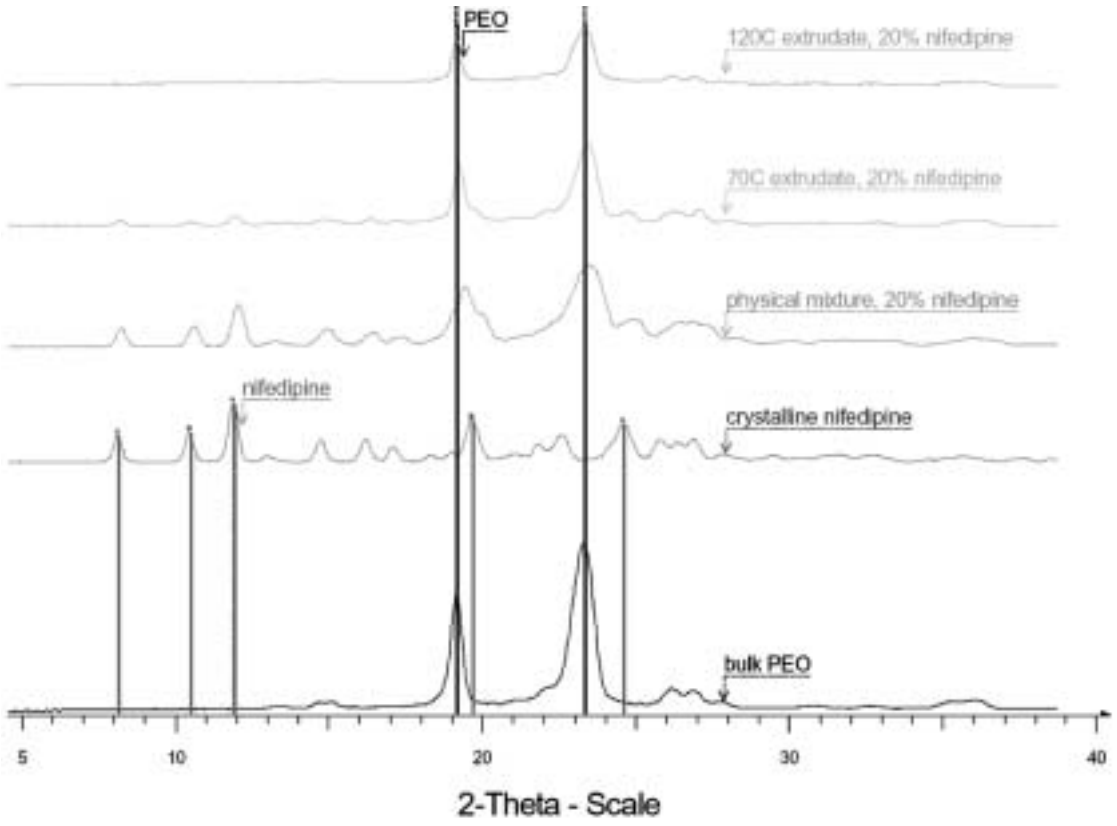

FIGURE 2 **XRD of Nifedipine, its Physical Mixture with PEO, and Extrudates.**

melted materials started to flow freely, became homogeneously distributed to cover the entire view field. During cooling, only one form of crystallization was observed at 44°C (Fig. 3g), which quickly spread to the whole view field with colorful crystal patterns. No other forms of crystallizations were observed. This visual observation again demonstrated that nifedipine and PEO became miscible at elevated temperature and stayed in a miscible state upon cooling to room temperature. Nascent crystalline structures of the drug completely disappeared, forming a drug-polymer dispersion.

SEM and Raman Imaging of Extrudes

To identify form changes in the solid dispersion system, the spectra of standard crystalline nifedipine and amorphous nifedipine were taken. The amorphous nifedipine was obtained by using a DSC ramp-up temperature at 10°C/min from 25°C to 190°C, then a quench down to 25°C. The comparison of two standard Raman spectra is shown in Fig. 4. The signature regions are 600–700 cm^{-1} (I), 1300–1400 cm^{-1} (II), and 1600 to 1700 cm^{-1} (III), where little PEO signal was present. In the Fig. 4 insets, it is clearly shown that amorphous nifedipine has a signature peak at 635.2 cm^{-1} in region I, while crystalline nifedipine has a high sharp peak at 1349.7 cm^{-1} (region II) and a peak at 1680.8 cm^{-1} (region III) (Chan et al., 2004).

The cross-sections of the extrudates processed at different temperatures were then observed under an optical microscope, and an image from a 70°C extrudate is shown in Fig. 5a. This matrix appeared to be rather homogeneous, although several cavities were visible. Magnified SEM images (Fig. 5b and c) zoomed into the homogeneous region and rough region with cavities revealed significantly different morphology between the two areas. Raman spectroscopy (Fig. 5d) also showed significant differences in the molecular structure between the homogeneous region and the cavity spots. The Raman scan in area II was almost identical to the scan of crystalline nifedipine, showing the signature peak at 1349.7 cm^{-1}, and with no PEO peak being present in this spectrum, whereas the Raman

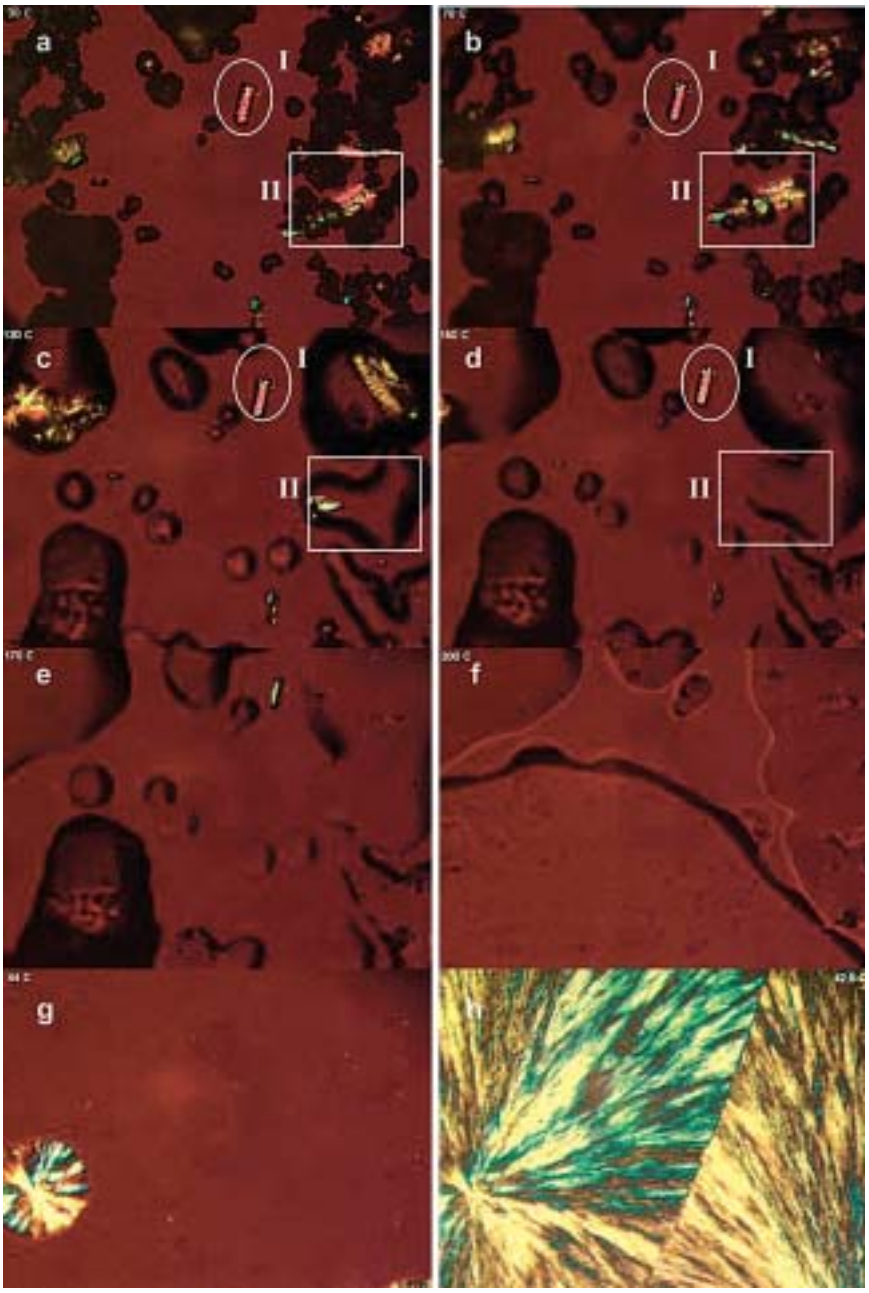

FIGURE 3 **Images of Nifedipine/PEO (1:4) Mixture Taken on a Hot-Stage Polarized Microscope. (a–f) Snapshots at Different Temperatures 30°C, 70°C, 130°C, 150°C, 170°C, and 200°C in a Ramp-up Process at a Rate of 10°C/min. (g–h) Snapshots at Temperatures of 44°C and 42.5°C in a Natural Cooling Process.**

spectrum in area I appeared more like a combination of PEO, amorphous nifedipine (clear peak at 635.2 cm^{-1} in Fig. 5d), and crystalline nifedipine (a small peak at 1349.7 cm^{-1}).

Extrudates formed at 120°C (Fig. 6a) show a more uniform morphology across the section, indicating good drug distribution. Raman spectra (Fig. 6d) obtained from zoomed areas of relatively smooth (area I in Fig. 6a and b) or rough regions (area II in Fig. 6a and c) indicated comparable shift and intensity, confirming uniform dispersion of nifedipine inside the PEO matrix. In the Raman spectra, both regions show a clear amorphous peak at 635.2 cm^{-1} and no peak present at 1680.8 cm^{-1}.

Hence, at a low processing temperature, PEO exhibits high viscosity such that drug diffusion in the polymer is limited, resulting in poor mixing

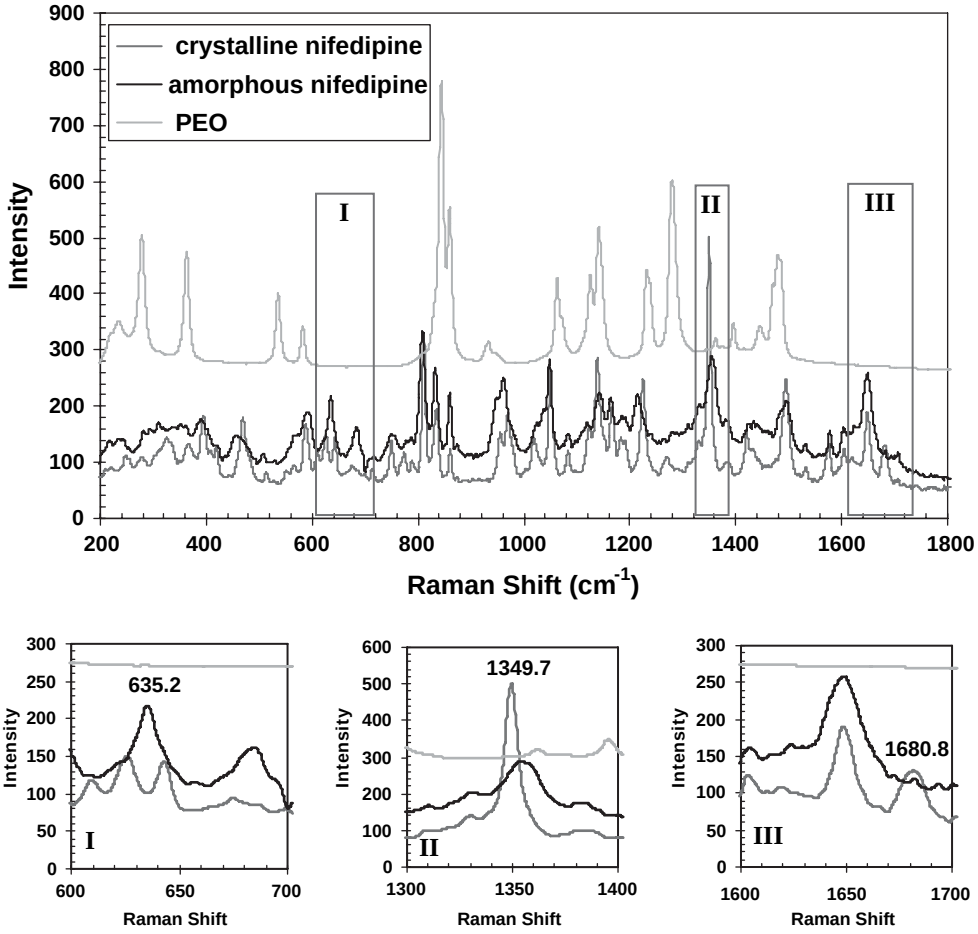

FIGURE 4 **Raman Spectra of Crystalline Nifedipine and Amorphous Nifedipine. The insets are Zoom-in Spectra in Signature Regions.**

during extrusion. Inside the observed cavities there appeared to be highly localized drug concentration, as confirmed by Raman. At a modestly high processing temperature of 120°C, the viscosity of PEO decreased enough to allow rapid drug diffusion and dissolution in the polymer, yielding in a well-dispersed system. Such a dispersion probably also created an optimal environment for better molecular interaction between the drug and PEO, where PEO facilitated the form change of crystalline nifedipine to amorphous nifedipine at a temperature far below its melting point. This is clearly supported by the new Raman shift at 635 cm^{-1} that is a characteristic feature of amorphous nifedipine. SEM and Raman spectroscopy, therefore, have clearly demonstrated uniform drug distribution in the matrix and that drug-PEO interaction at a molecular level helped the drug to stay in the amorphous form for extrudes processed at 120°C and above.

Stability Study

The extrudates kept the original shape and integrity during the stability study. The weight changes were negligible, indicating a limited amount of water absorption.

Nifedipine appeared to be chemically stable when the extrudates were stored at 25°C/60% RH and 40°C/75% RH for 6 months. Potency change was less than 1% by assay. However, conversion from the amorphous to the crystalline drug form appeared to have occurred. A comparison between the initial extrudate and that after 3 months of stability study is shown in Fig. 7. Recrystallized nifedipine peaks are clearly visible, although their intensity (peak height) appeared to be less than 25% of the physical mixture. This finding appears to be true for extrudates formed at either 70°C or 120°C.

Further study using SEM (Fig. 8) revealed rather fine particles of the recrystallized nifedipine embedded in the matrix, primarily in the form of fine

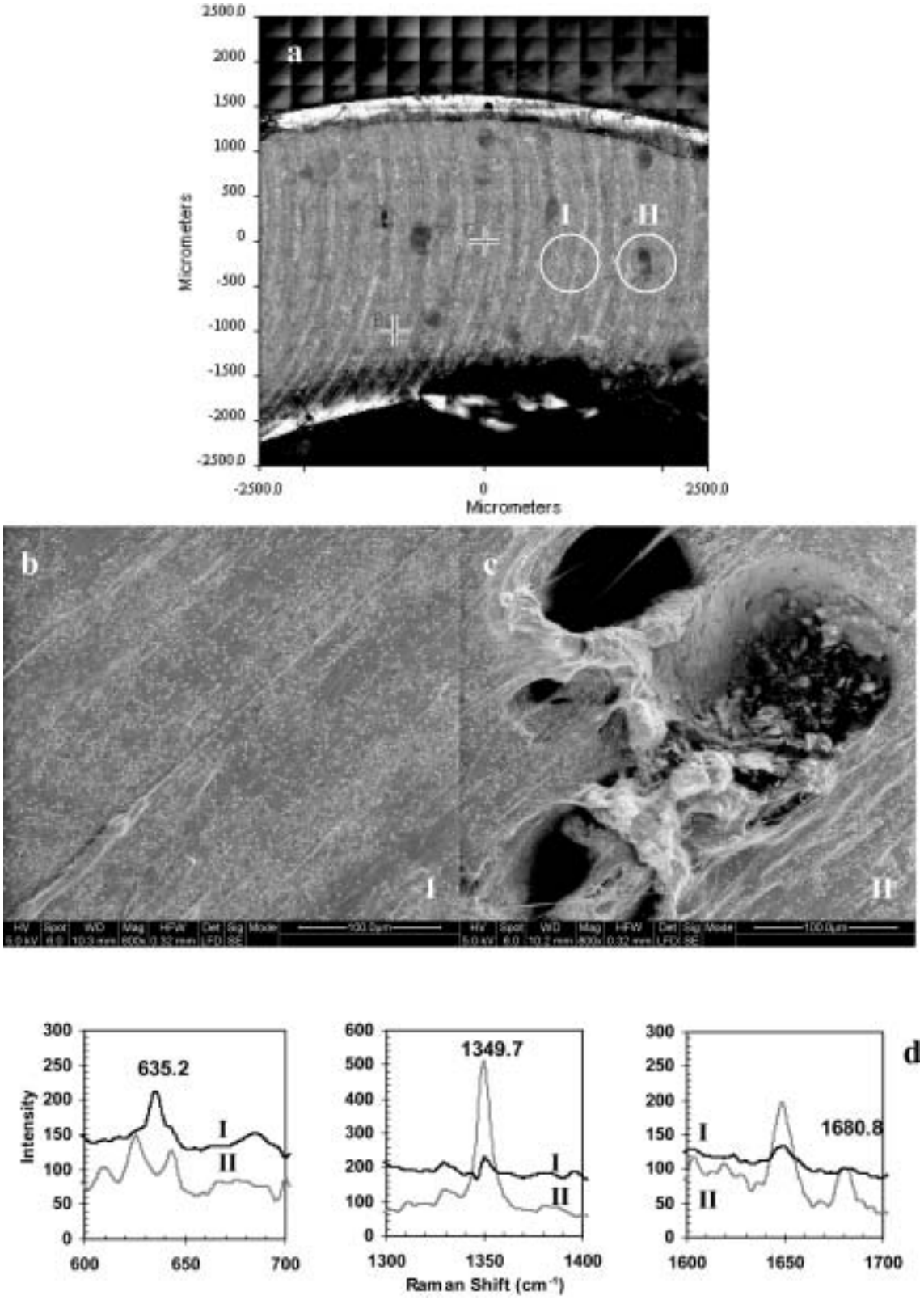

FIGURE 5 **Characterization of Drug Homogeneity in Extrudates Processed at 70°C. (a) Optical Microscopic Image of a Cross-Section. I and II Represent Homogeneous and Rough/Cavity Areas, Respectively. SEM Images of Magnified I (homogeneous) Area (b) and II (rough and Cavity) Area (c). (d) Raman Comparison of areas I and II.**

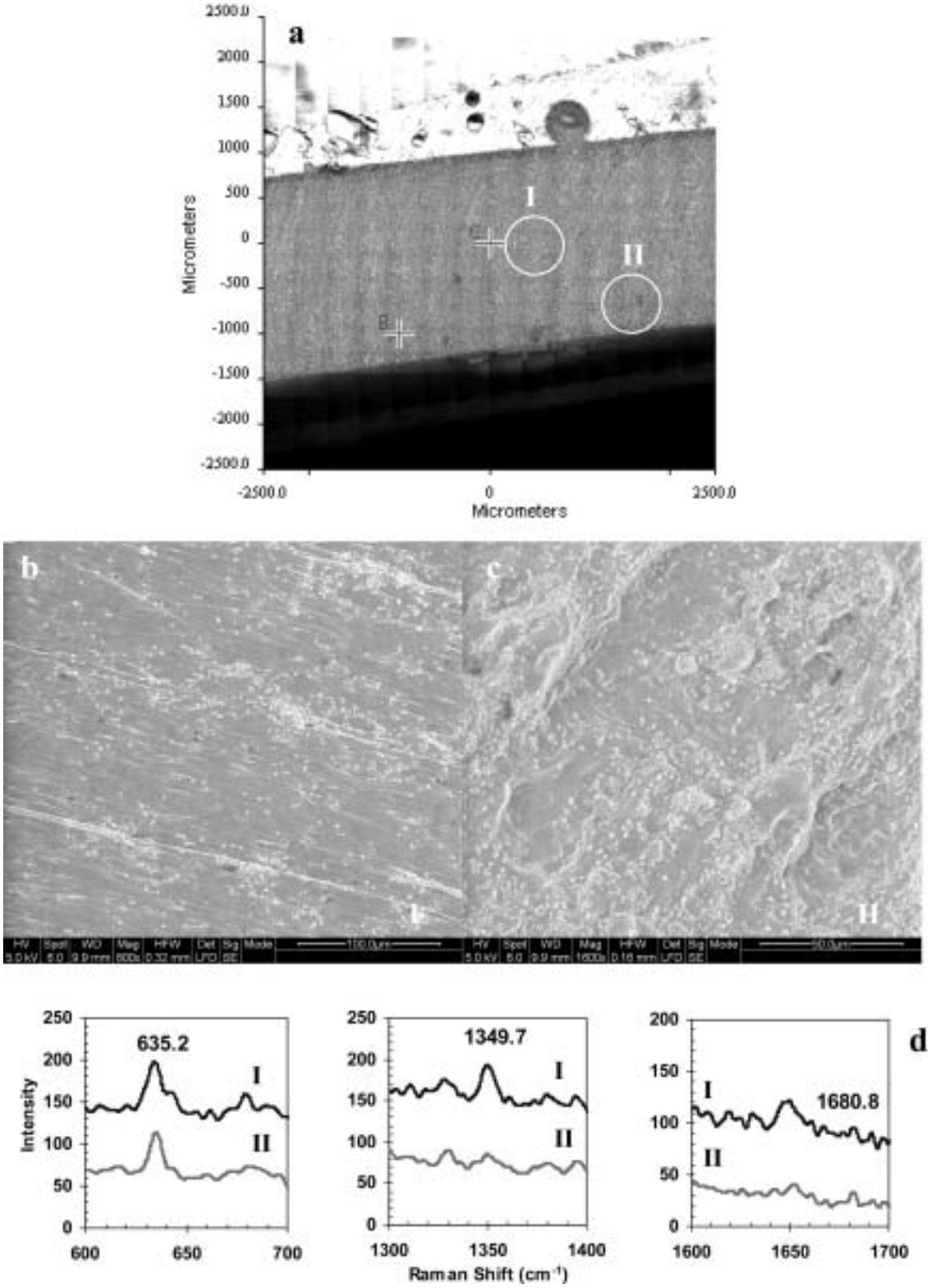

FIGURE 6 **Characterization of Drug Homogeneity in Extrudates Processed at 120°C. (a) Optical Microscopic Image of a Cross-Section. I and II Represent Homogeneous and Rough Areas, Respectively. (b and c) SEM Images of Magnified I and II Areas. (d) Raman Comparison of areas I and II.**

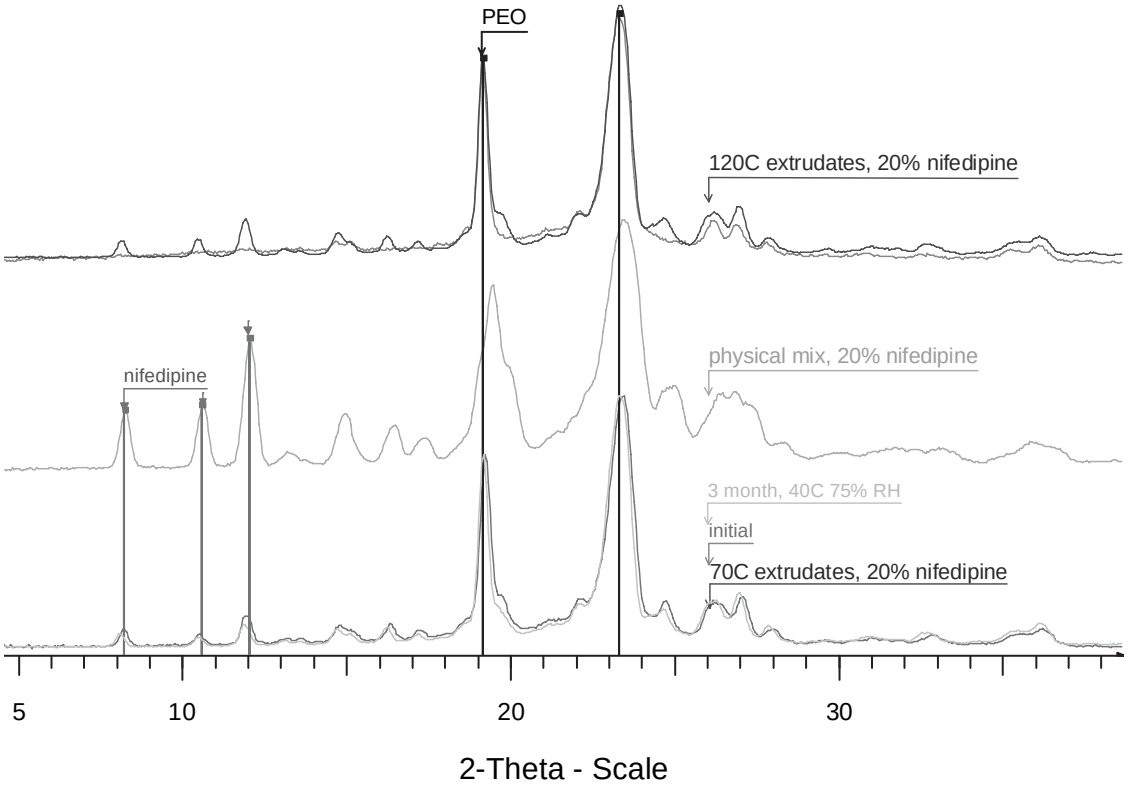

FIGURE 7 **XRD of Initial Extrudates and 3 Months at 40°C/75% RH, in Comparison to the Physical Mixture.**

needles (less than 5 μm), while the original crystals were 20–50 μm.

Dissolution Enhancement

Dissolution profiles of drug from milled powders are shown in Fig. 9. While pure drug and the physical mixture dissolved slowly over the 120-minute time frame, extrudates reached a plateau concentration in 10 minutes or less. In addition, the saturation concentration was approximately twice as high compared to pure crystalline nifedipine or the physical mixture. The difference, if any, between extrudates processed at different temperatures appeared to be negligible. Even with localized regions of crystalline drug being presented in the extrudates, the overall contribution of such crystals on dissolution might be limited, as demonstrated by the small peaks in XRD (Fig. 2, less than 5% by peak height). Hence, dissolution could be dominated by the amorphous drug. Another explanation is that the dissolving PEO in the extrudate might facilitate drug dissolution. The observed dissolution improvement makes polymers such as PEOs valuable platforms for absorption enhancement of poorly soluble drugs.

CONCLUSIONS

A solid dispersion system of nifedipine and PEO has been generated through a hot-melt extrusion process. Extrudate characterization by DSC and XRD confirmed the loss of drug crystallinity at processing temperatures as low as 120°C. Further SEM and Raman studies confirmed drug dispersion within and interaction with PEO, facilitated by a higher processing temperature. Partial conversion to the crystalline state was observed during stability test. Extrudates exhibited much improved drug dissolution. Such a drug/PEO solid dispersion system can potentially be used for solubility enhancement of poorly soluble compounds. A relatively low processing temperature adds an additional advantage for this polymer.

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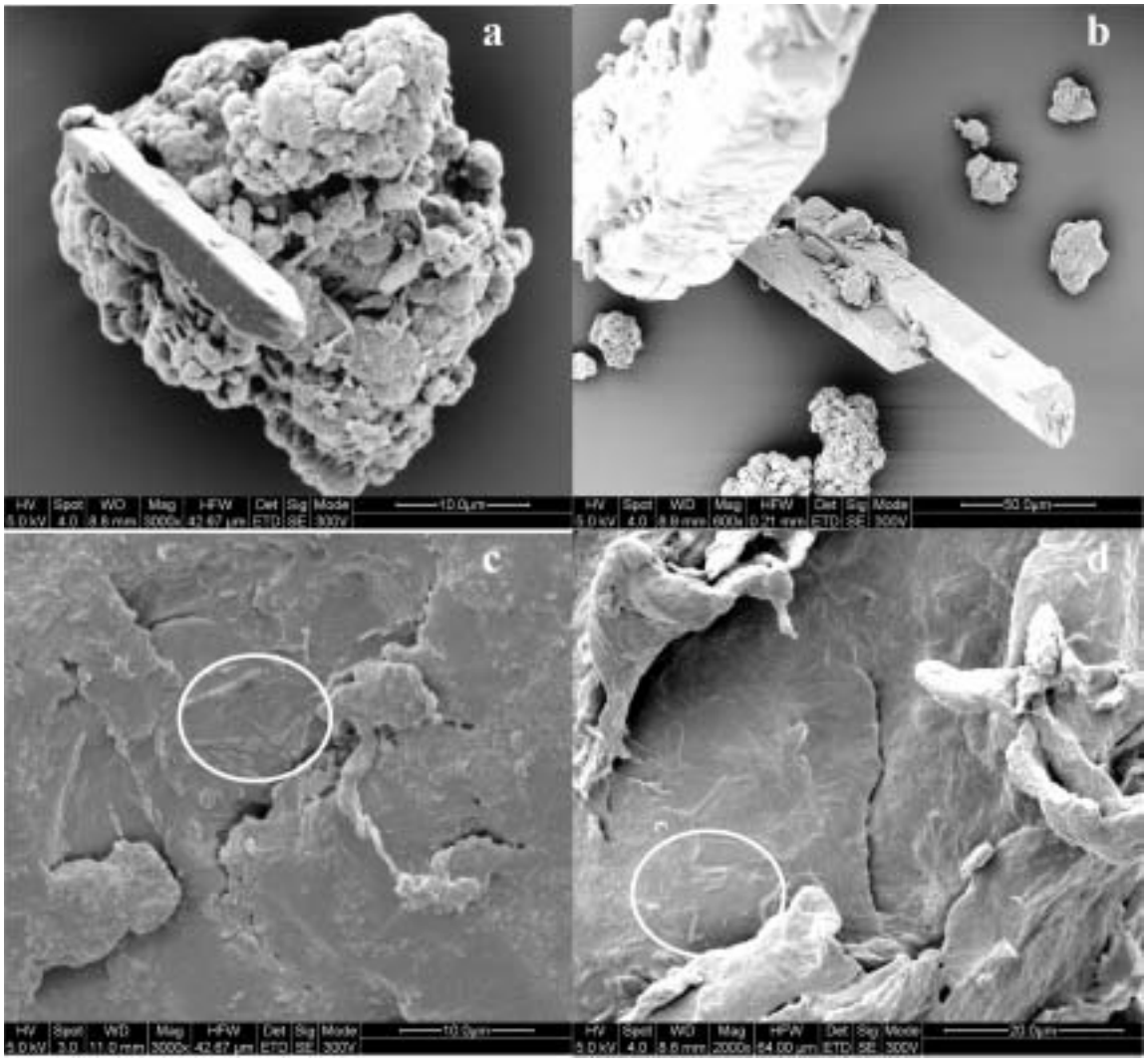

FIGURE 8 **SEM Images of Physical Mixture of Nifedipine and PEO (a and b), Extrudate Processed at 70°C (c), and Extrudate Processed at 120°C (d) after 3 Months' Storage at 40°C/75% RH. Circle Areas Shown Tiny Crystals Being Formed.**

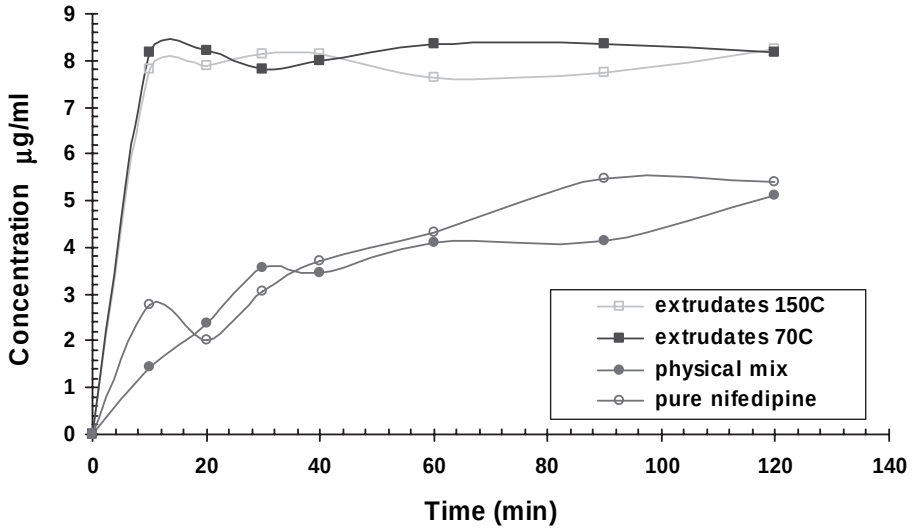

FIGURE 9 **Dissolution Profiles of Cryo-Milled Extrudates Processed at 70°C and 120°C, Physical Mixture, and Pure Crystalline Drug in 0.05 M pH 6.8 Phosphate Buffer.**

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