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ScienceDirect
International Journal of Pharmaceutics 355 (2008) 141–149
INTERNATIONAL JOURNAL OF PHARMACEUTICS
www.elsevier.com/locate/ijpharm

Evaluation of solid state properties of solid dispersions prepared by hot-melt extrusion and solvent co-precipitation

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Received 18 June 2007; received in revised form 7 October 2007; accepted 4 December 2007
Available online 23 December 2007

Abstract

The solid state properties of solid dispersions of Compound A in hypromellose acetate succinate (HPMC-AS) prepared by hot-melt extrusion (HME) and solvent co-precipitation (CP) processes were evaluated using powder X-ray diffractometry (PXRD), thermal analysis, optical microscopy, scanning electron microscopy (SEM), FT-IR and Raman spectroscopy, water vapor sorption analyzer, and surface area by BET. PXRD indicated that both processes converted the crystalline drug into amorphous solid dispersions with a glass transition temperature around 104–107 °C and both products have similar spectroscopic and hygroscopic properties. The two products have similar true densities; however, the CP product is more porous and has a larger specific surface area than the HME product, as indicated by the BET results and SEM micrographs. Dissolution study using USP apparatus 2 showed that the CP product had a faster dissolution profile, but slower intrinsic dissolution rate than the HME product. The two products have acceptable physical stability after storage in 40 °C/75% RH chamber for 3 months. However, the HME product is more stable than the CP product in aqueous suspension formulation.

Keywords: Solid dispersion; Hot-melt extrusion; Solvent co-precipitation; Physical characterization

1. Introduction

With the implementation of high-throughput screening in the pharmaceutical industry, a significant number of poorly water-soluble compounds are identified. Consequently, innovative pharmaceutical technologies are being developed to enhance absorption and bioavailability of these compounds. Solid dispersion technologies (Serajuddin, 1999) have been widely used in both pre-clinical and clinical formulation development as a successful approach to deliver insoluble compounds and improve exposure in both experimental animals and human subjects. There are a variety of approaches to prepare solid dispersion using polymers as carriers, such as hot-melt extrusion (HME), spray drying, and solvent co-precipitation (CP). With test compounds being highly dispersed in the polymer matrix (usually at the molecular level or in microcrystalline phase), solid dispersion systems provide a large surface area of the compounds for dissolution process, which greatly improves the dissolution. Therefore, the absorption of these compounds can be improved, if intestinal permeability is not the limiting factor, *i.e.* biopharmaceutical classification system (BCS) class 2 compounds (Amidon et al., 1995). The amorphous or the microcrystalline API in solid dispersion is more stable than its pure form in the same physical state due to the interaction between the polymer and active pharmaceutical ingredient (API) molecules in solid dispersion (Matsumoto and Zografi, 1999). Previously, poorly soluble compounds such as nimodipine (Zheng et al., 2007), nifedipine (Li et al., 2006), itraconazole (Miller et al., 2006), and indomethacin (Chokshi et al., 2005; Zhu et al., 2006) were dispersed in polymers using HME process. The physico-chemical and mechanical properties of these products were characterized. In addition, the CP process was also reported of being used to prepare solid dispersions of poorly soluble compounds (El-Gazayerly, 2000; Sertsou et al., 2002a,b). However, there was no direct comparison on the physico-chemical properties of the products manufactured from HME and CP processes.

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doi:10.1016/j.ijpharm.2007.12.017

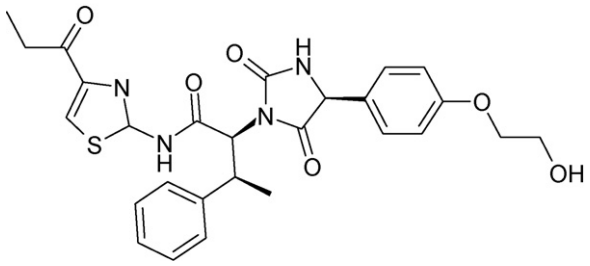

Fig. 1. Molecular structure of Compound A.

Hypromellose acetate succinate (HPMC-AS) is an enteric coating material for enteric or sustained release formulations. It is also used in solid dispersion technology for poorly water-soluble compounds to improve bioavailability. With various contents of acetyl and succinoyl groups in the polymer, there are several types of HPMC-AS, which dissolve at different pH levels. Type L has a high ratio of succinoyl substitution (content: 15%) to acetyl substitution (content: 8%) (S/A ratio), while type H has a low S/A ratio (succinoyl content: 6%; acetyl content: 12%) and type M has a medium S/A ratio (succinoyl content: 11%; acetyl content: 9%). With a high S/A ratio, type L HPMC-AS starts to dissolve at a lower pH (pH $\geq$ 5.5), compared with type M (pH $\geq$ 6.0) and type H (pH $\geq$ 6.8), which start to dissolve at higher pH. HPMC-AS is also available in fine (mean particle size: 5 μm) and granular (mean particle size: 1 mm) particle sizes (Shin-Etsu Chemical Co., Ltd.). HPMC-AS Grade AS-LF, where F designates the fine powder form, was used in this work.

In this research, a model Compound A (Fig. 1, molecular weight: 536.6) was assessed for formulation development using HME and CP technologies with HPMC-AS. Compound A belongs to BCS class 2 category, with a poor solubility (~0.2 μg/ml in 50 mM pH 6.8 phosphate buffer) and a high permeability (>10×10^{-6} cm/s in Caco-2 cells). Detailed characterizations were performed using a variety of techniques and their physical stability was evaluated to better understand the physico-chemical properties of the HME and CP products of Compound A.

2. Materials, instrumentation and methods

2.1. Materials

HPMC-AS (Grade AS-LF, Lot# 409069) was provided by Shin-Etsu Chemical Co., Ltd. Crystalline Compound A hydrate was synthesized in-house.

2.2. Instrumentation and methods

2.2.1. Preparation of HME product

The HME product was prepared using a hot-melt extruder (Micro 18 PH, American Leistritz Extruder Corporation, Somerville, NJ, United States) at elevated temperature. After cooling to room temperature, the product was milled and passed through 40 mesh sieve for further use.

2.2.2. Preparation of CP product

The CP product was prepared by precipitation of Compound A and HPMC-AS from their solution and was dried under vacuum. The CP product was also milled and passed through 40 mesh sieve prior to use. Both the HME and the CP products have the same drug loading (40% by weight).

2.2.3. Physical characterization of the HME and CP products

Both products were characterized by the following instruments and techniques in parallel.

Differential scanning calorimetry (DSC 7, Perkin-Elmer Inc., Wellesley, MA, United States) and thermogravimetry (Pyris 1 TGA, Perkin-Elmer Inc., Wellesley, MA, United States) were used for thermal analysis with a nitrogen purge at 30 ml/min and a heating rate of 10 °C/min. Hermetic pans carrying a pin hole were used with sample weight around 5 mg for DSC and open pans were used for TGA with sample weight about 10 mg.

An advanced diffraction system (Scintag Inc., Cupertino, CA, United States) was used to collect powder X-ray diffraction (PXRD) spectra with a CuKα source. The scan was from 2° to 40° 2θ with a step size of 0.02° and the residence time of 1.2 s.

A polarized microscope (Leitz Aristomet, Leitz, Germany) was used to examine crystallinity as well as particle size of the products. The micrographs were taken at 100× magnification.

A LEO 1530 VP near-field scanning electron microscopy (SEM, LEO Electron Microscopy Group Ltd., Cambridge, United Kingdom) was used to examine the morphology and surface features of the products. All samples underwent sputtering coating with carbon prior to the characterization. The micrographs were taken under 1–2 kV with a working distance ranging between 3 and 5 mm at room temperature.

A water vapor sorption analyzer (model SGA-100, VTI Corporation, Hialeah, FL, United States) was employed to assess the hygroscopicity of both products at 25 °C with a sample size of around 15 mg. The experiments were performed under a relative humidity (RH) cycle of 10% → 90% → 10% at the step of 10%. The equilibrium criterion was set at 0.01% weight change in 2 min or maximum 300 min equilibrium time.

An FT-IR spectrometer (Nicolet Nexux 870, Thermo Electron Corporation, Waltham, MA, United States) attached with a FT-Raman module and Smart Orbit accessory was used to collect FT-Raman and FT-IR spectra via OMNIC software. The FT-Raman spectra were collected between 200 and 3700 cm^{-1} with a resolution of 4 cm^{-1} and 500 scans and the FT-IR spectra were collected between 600 and 4000 cm^{-1} with a resolution of 4 cm^{-1} and 128 scans.

A Distek dissolution apparatus (Distek Dissolution System 2100A, Distek Inc., North Brunswick, NJ, United States) was used to determine both dissolution and intrinsic dissolution rate (IDR) of the CP and HME products in 500 ml 1% sodium lauryl sulfate (SLS) 50 mM phosphate buffer (pH 6.8) at 37 °C with a stirring rate of 50 rpm. For dissolution test, 100 mg of the CP or HME product was suspended in 1 ml aqueous vehicle (2% hydroxypropyl cellulose) and then transferred to the dis-

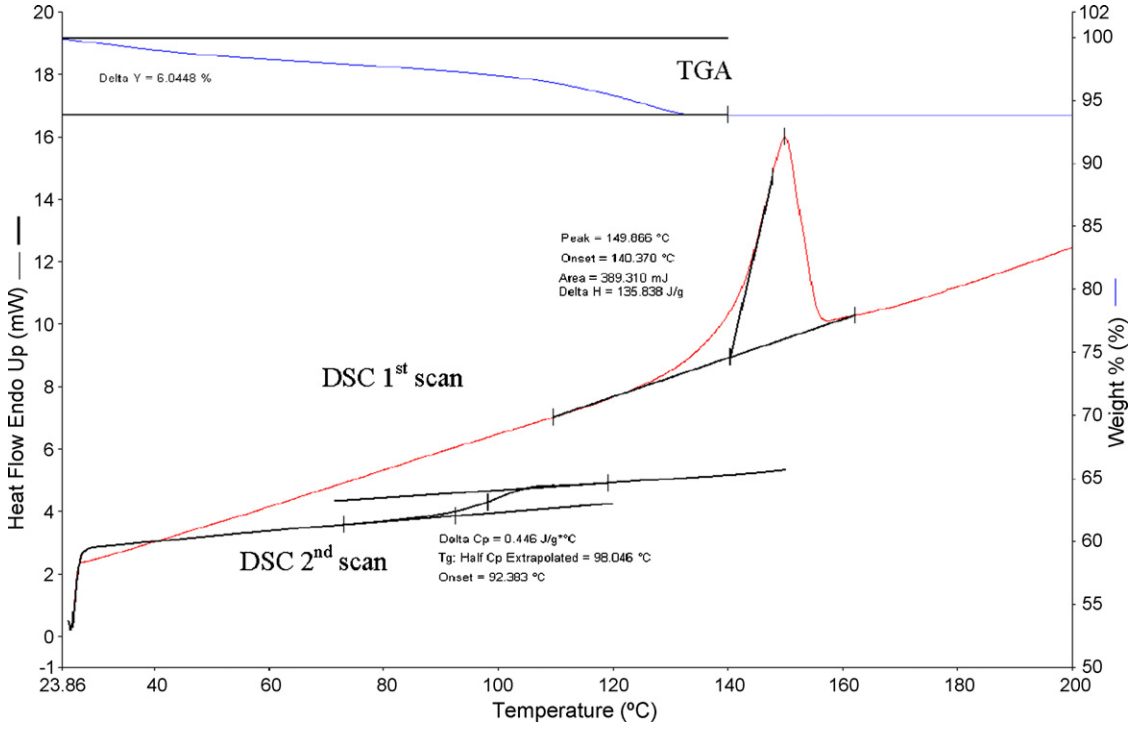

Fig. 2. Thermal analysis of Compound A.

solution media for measurement. The intrinsic dissolution rate (IDR) was measured using constant surface area pellets in Distek dissolution apparatus. The powder was compacted into pellets under 2000 pounds using a Carver press (Carver, Inc., Wabash, IN, United States) for the experiment with a dissolution surface area of 0.5 cm^2. After experiments, the pellet surface was examined by PXRD and polarized microscopy. For both dissolution and intrinsic dissolution measurements, a UV spectrometer (detection wavelength at 230 nm) was attached to the dissolution system and auto-sampling probes were positioned in the dissolution beakers with filters (45 μm) fitted on the tip.

A TriStar 3000 surface area analyzer and an AccuPyc 1330 pycnometer (Micromeritics Instrument Corporation, Norcross, GA, United States) were utilized to measure the specific surface area and true density, respectively. The specific surface area was determined by the multiple-point BET method using nitro-

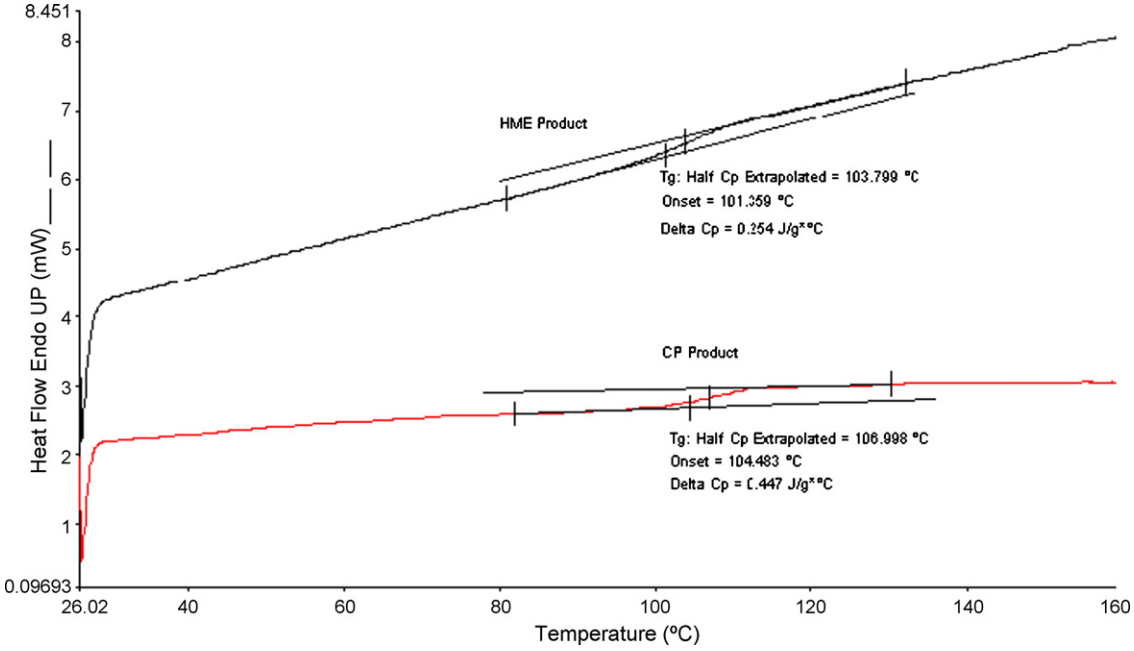

Fig. 3. DSC results of the HME and CP products.

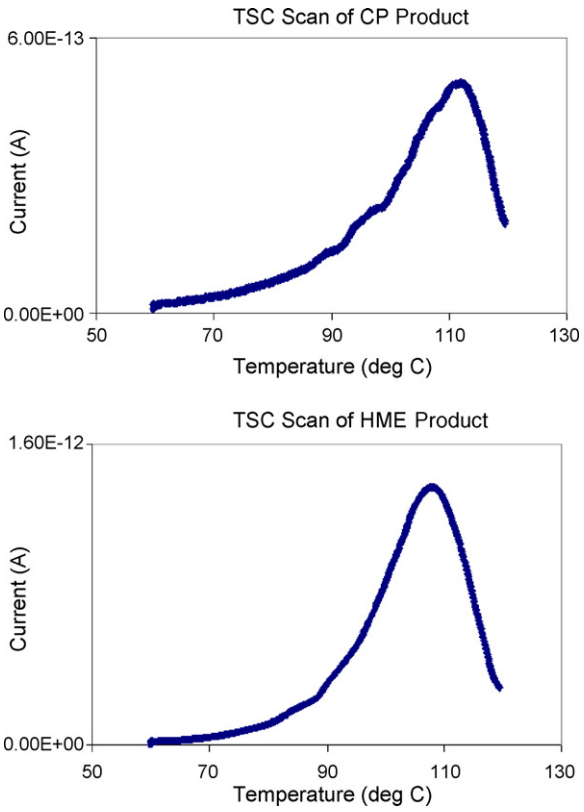

Fig. 4. TSC results of the HME and CP products, showing the T_g at 109 °C for both products.

gen gas as the adsorbate. Helium gas was used for true density measurement.

Thermally stimulated current (TSC) analysis was used to determine the T_g of the two products using a Ther-Mold TSC/RMA instrument (Setaram Instrumentation, Caluire, France). In the experiments, the samples were heated to 110 °C and subjected to an electric field of 100 V/mm for 2 min for polarization and then cooled to 60 °C at 2 °C/min in the electric field. After the electric field was removed, the temperature was held at 60 °C for 1 min. The samples were then heated to 120 °C at 7 °C/min and the depolarization current was measured simultaneously as a function of temperature.

2.2.4. Physical stability of the HME and CP products

The suspensions of the HME and CP products were prepared in an aqueous vehicle (2% hydroxypropyl cellulose) at 25 mg/ml concentration. After agitation for 1, 4 and 7 days, the suspensions were collected and filtered. Upon drying, the products were characterized using PXRD. In addition, the two products were stored in 40 °C/75% RH chamber for 3 months to monitor potential crystallization of Compound A from the products using PXRD.

3. Results and discussion

The hydrate of Compound A was characterized using thermal analysis. DSC (Fig. 2) showed a melting event at 150 °C in an aluminum hermetic pan without any other observable thermal events. After melting, the sample was cooled to 25 °C in the DSC cell and the scan was repeated. The second scan indicated the formation of amorphous phase of Compound A with a glass transition temperature at 98 °C, after it melted and was cooled to 25 °C. In TGA, the sample showed a total weight loss of 6.04% at elevated temperature, suggesting the presence of bound water in the crystal lattice.

Through CP and HME processes, two solid dispersion products were prepared. In DSC, the CP and HME products have similar glass transition temperatures at 107 °C and 104 °C, respectively (Fig. 3). However, the CP product has a higher ΔC_p (0.447 J/g °C) than the HME product (0.254 J/g °C). The glass transition temperatures of both products were determined to be

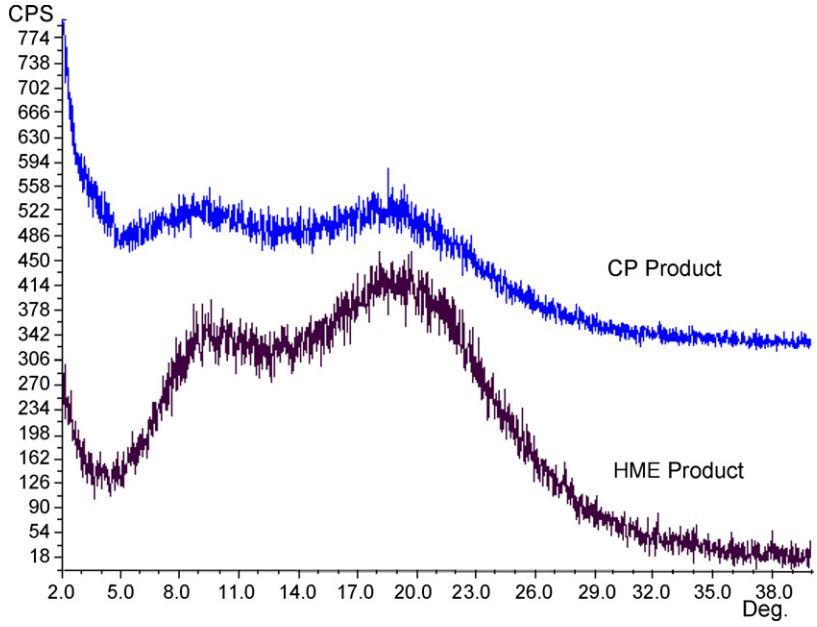

Fig. 5. PXRD patterns of the HME and CP products indicating their amorphous nature.

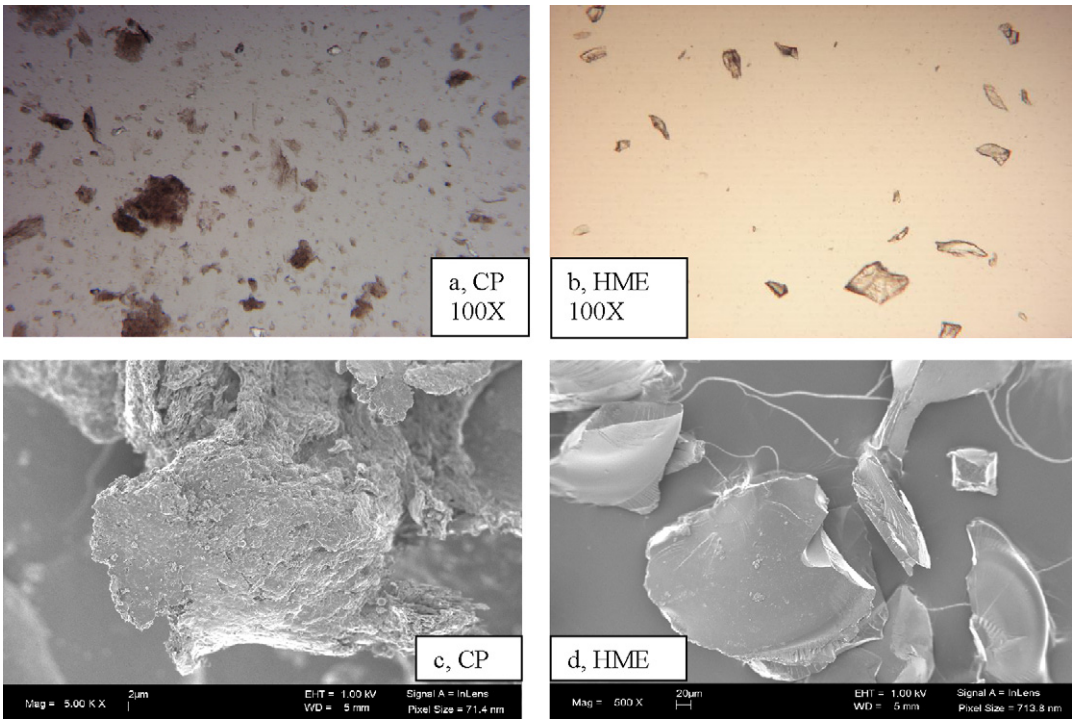

Fig. 6. Microscopic photos (100×) and SEM micrographs of the HME and CP products.

~109 °C by TSC (Fig. 4). The TSC scan started with sample polarization in the electric field at 110 °C, which was slightly higher than the T_g measured by DSC. This pre-treatment in TSC may remove the thermal history of the samples and therefore both CP and HME products showed similarly higher T_g in TSC than in DSC.

In agreement with the DSC results, the PXRD results (Fig. 5) indicated that both CP and HME products are amorphous. Both PXRD diffraction patterns have a halo hump at around 18° 2θ. The lack of sharp diffraction peaks suggests lack of crystallinity of the products.

Under polarized microscope, neither of the two products showed any birefringence (Fig. 6a and b). The particle morphology of the CP product is flake-like. However, the HME product appears as glass-like particles with an irregular shape. The SEM micrographs (Fig. 6c and d) of the two products indicated that CP process produced porous particles with rough surfaces, while HME process produced particles with smooth surfaces and sharp edges. According to the BET results, the CP product had a specific surface area of 6.19 m^2/g compared with 0.13 m^2/g for the HME product, which confirms the surface properties observed in the SEM micrographs. However, the two products have comparable true densities with 1.33 g/cm^3 for the CP product and 1.30 g/cm^3 for the HME product.

Water vapor sorption/desorption experiments suggested that the two products have similar overall hygroscopicity (Fig. 7). In addition, under microscopic examinations, no crystallization of Compound A occurred in the samples after experiments. However, in the adsorption isotherm, the CP product took up slightly more water than the HME product. There was no significant difference in the desorption isotherm between the two products. Considering the much larger specific surface area of

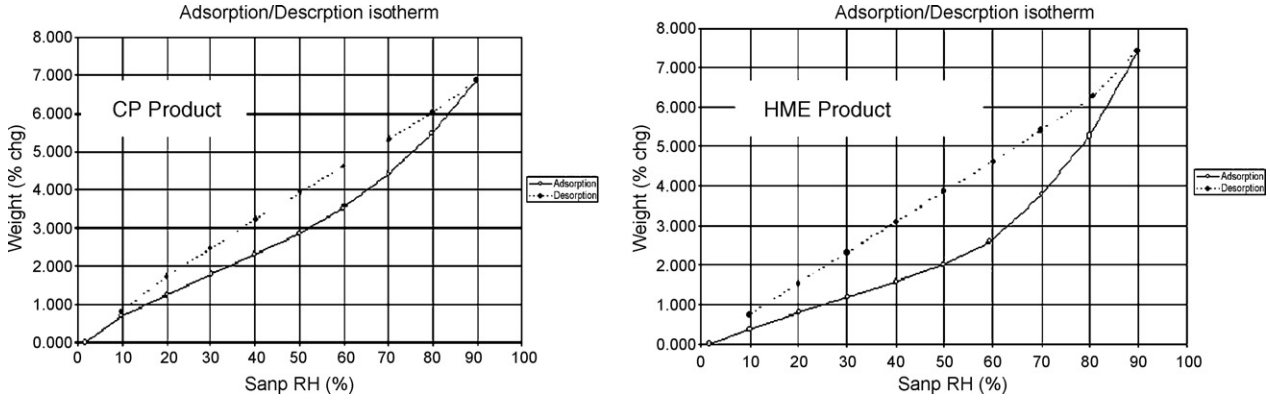

Fig. 7. Water vapor sorption/desorption behavior of the HME and CP products.

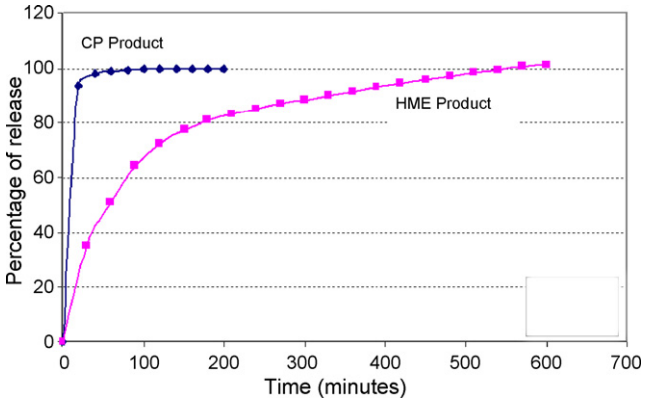

Fig. 8. Dissolution results of the HME and CP products using USP paddle method.

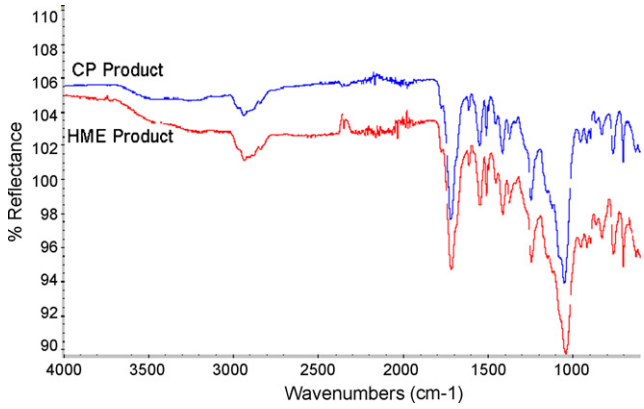

Fig. 10. FT-IR spectra of the HME and CP products.

the CP product, unexpectedly, there was less moisture per surface square unit. One possible explanation may be that the CP process involves a solution, where both the drug and the polymer are dissolved, followed by precipitation. In the solution, the fully extended polymer chains are likely to have strong inter-molecular interactions with the API molecules. During the precipitation and in the final product, the molecular level interactions may be trapped and remain in the bulk powder, which occupies the active functional groups that are hygroscopic. However, HME process begins with a powder blend, followed by fusion and mixing in the extruder, where less molecular level interaction occurs, therefore leaving more active functional groups open for moisture adsorption (Crowley and Zografi, 2002). However, this slight difference between the two products cannot be distinguished by DSC or spectroscopic tools as shown in this work.

The dissolution was conducted using USP paddle method in 500 ml 1% SLS 50 mM phosphate buffer, pH 6.8. The CP product had much faster dissolution than the HME product, apparently due to the difference in specific surface area (Fig. 8). It took about half an hour to achieve 100% release for the CP product, compared with eight hours for the HME product. Using the same experimental conditions, the IDR (Fig. 9) was determined as 0.040 ± 0.006 and 0.070 ± 0.003 mg/min/cm^2 for the CP and HME products, respectively. In addition, after intrinsic dissolution experiments, the pellet surfaces for both products were examined by PXRD and microscopy and the results indicated no crystallization. The fast intrinsic dissolution rate of the HME product compared to the CP product is somewhat unexpected. However, the difference may be due to the stronger interactions between the polymer and the API in the CP product than the HME product, which causes less surface water activity of the former and therefore, lower intrinsic dissolution rate. Attempts were made to determine the intrinsic dissolution rate of Compound A, but it was unsuccessful due to the extremely low solubility.

FT-IR (Fig. 10) and FT-Raman (Fig. 11) spectra were collected for the two products, and they are not distinguishable based on this result. Due to the lack of crystallinity of Compound A in the dispersions, these two techniques may not be sensitive enough to show the difference between the HME and CP products.

After one day under ambient conditions, as indicated by the appearance of small diffraction peaks (Fig. 12), Compound A started to crystallize in the CP product in the aqueous suspension (2% hydroxypropyl cellulose). However, no crystallization was observed in the HME product. For reference, it was determined that the limit of detection for PXRD to observe the existence of crystalline Compound A in HPMC-AS is 2%. While crystallization continued in the CP product after 4 days in aqueous suspension, one small diffraction peak was seen with the HME product, suggesting the occurrence of crystallization of Com-

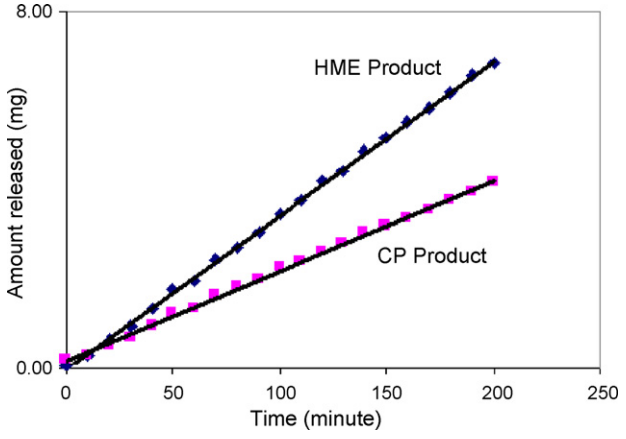

Fig. 9. Intrinsic dissolution rate determination of the HME and CP products using USP method.

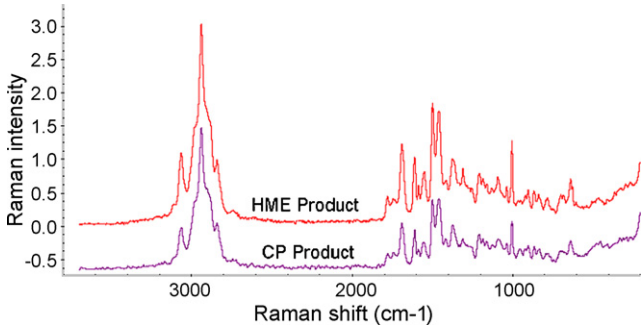

Fig. 11. FT-Raman spectra of the HME and CP products.

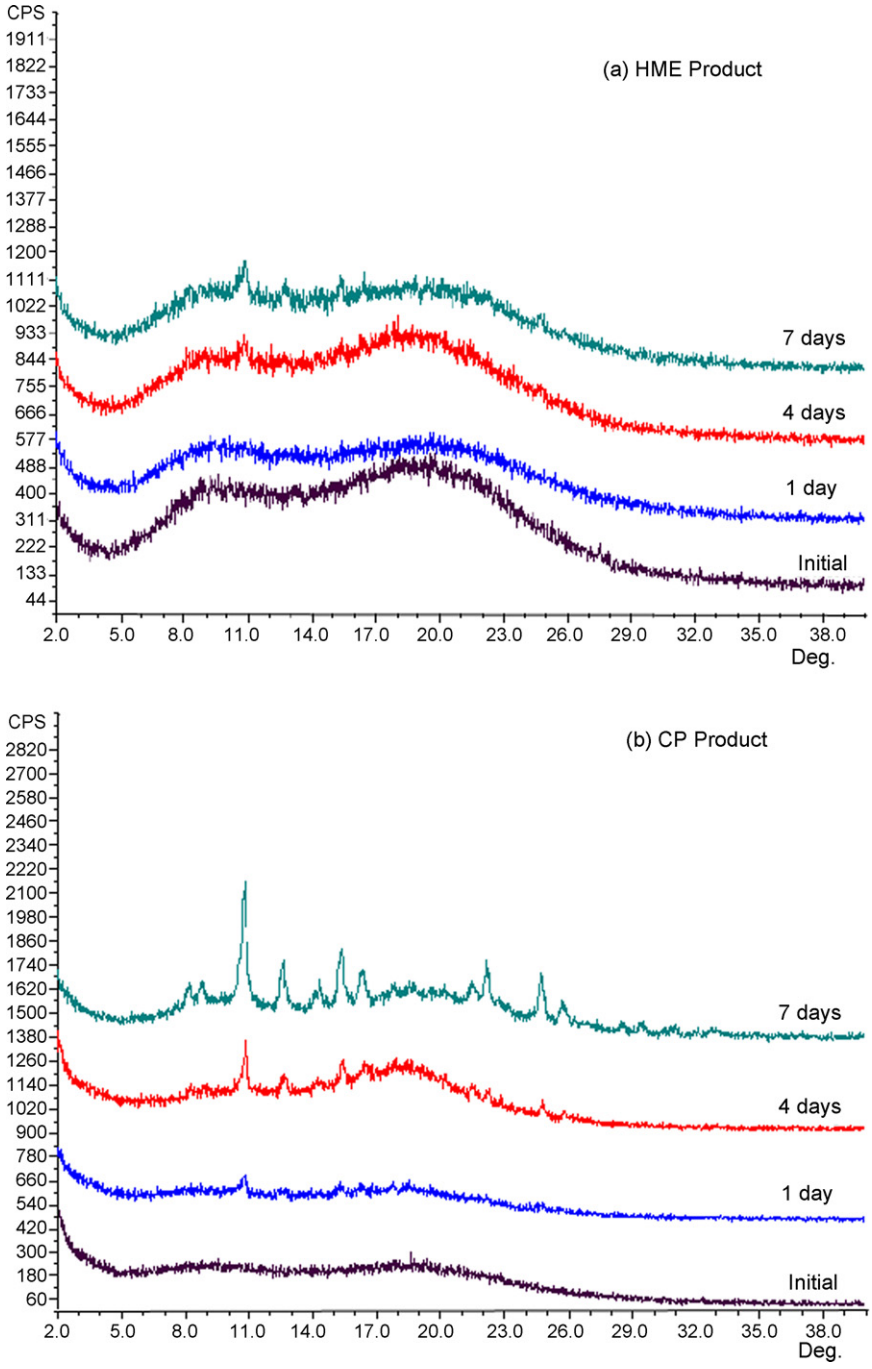

Fig. 12. PXRD patterns of the HME (a) and CP (b) products in suspension for 7 days.

pound A. More peaks appeared after seven days and the peak intensities became stronger in both products. Based on these observations, it is obvious that the HME product has better physical stability than the CP product in suspension. However, in the 40 °C/75% RH chamber, the two products did not show any sign of crystallization up to three months (Fig. 13). The better physical stability of the HME product is likely due to its less surface area, which causes less penetration of the water molecules into bulk particle and consequently, less plasticizing effect due to the presence of water as well as slower crystallization (Tong and Zografi, 2004).

Based on the above results, the CP and HME products can be adequately characterized using various analytical techniques. The two products were found to behave similarly when characterized using the following techniques and experiments: PXRD, water vapor sorption/desorption, TSC, FT-IR and Raman spectroscopies, true density measurement, and three-month solid state stability. However, differences were observed with respect to their physico-chemical properties using optical microscopy, SEM, specific surface area, dissolution and intrinsic dissolution rate, glass transition temperature in DSC, and suspension stability.

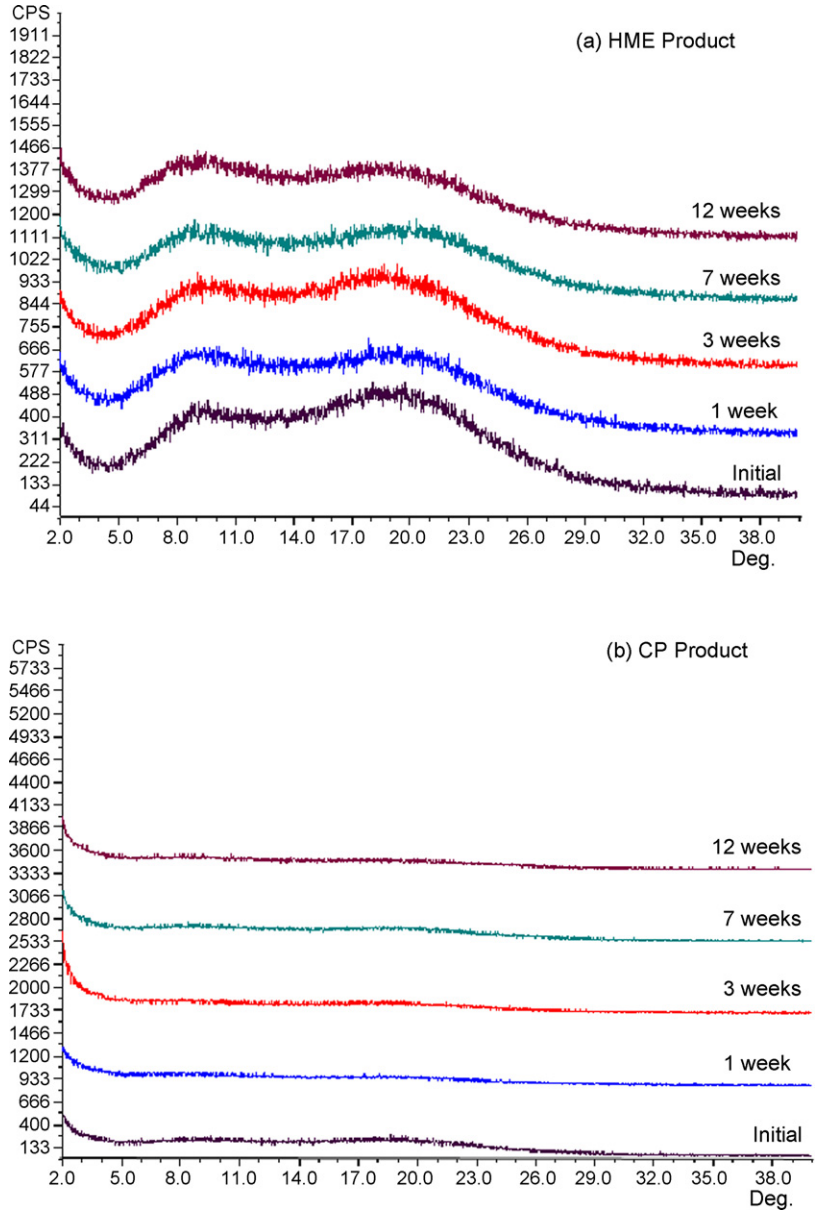

Fig. 13. PXRD patterns of the HME (a) and CP (b) products before and after storage in 40 °C/75% RH for 3 months.

4. Conclusion

Both CP and HME processes produced amorphous solid dispersions of Compound A which have the following in common: spectroscopic properties, powder X-ray diffraction, true density, and water vapor sorption/desorption behavior. In addition, the API was uniformly dispersed in both products as indicated by the single glass transition temperature in DSC thermographs. However, CP process produced solid dispersion with larger specific surface area due to its high porosity and rough particle surface, which provided a faster dissolution compared with the HME process. Although both bulk products showed acceptable physical stability for three months in the 40 °C/75% RH chamber, the CP product is physically less stable in suspension, which was due to the surface area difference.

Acknowledgement

The authors would like to thank Dr. Wantanee Phuapradit for kindly reviewing the manuscript as well as helpful discussions.

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