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A compaction process to enhance dissolution of poorly water-soluble drugs using hydroxypropyl methylcellulose

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Abstract

The purpose of this study was to develop a technique to enhance the dissolution rate of poorly water-soluble drugs with hydroxypropyl methylcellulose (HPMC) without the use of solvent or heat addition. Three poorly water-soluble drugs, naproxen, nifedipine, and carbamazepine, were studied with low-viscosity HPMC USP Type 2208 (K3LV), HPMC USP Type 2910 (E3LV and E5LV), and methylcellulose. Polymer and drug were dry-blended, compressed into slugs on a tablet press or into ribbons on a roller compactor, and then milled into a granular powder. Dissolution testing of the milled powder was performed on USP Apparatus II, 100 rpm, 900 ml deionized water, 37 °C. Drug distribution vs. particle size was also studied. The compaction processes enhanced drug dissolution relative to drug alone and also relative to corresponding loosely mixed physical mixtures. The roller compaction and slugging methods produced comparable dissolution enhancement. The mechanism for dissolution enhancement is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution. The compaction methods in this study may provide a lower cost, quicker, readily scalable alternative for formulating poorly water-soluble drugs.

Keywords: Hydroxypropyl methylcellulose; Poorly water-soluble; Drug dissolution; Roller compaction

1. Introduction

In recent years, an increasing number of active agents possess low aqueous solubility. As a result, oral delivery of poorly water-soluble drugs often results in low bioavailability since the rate-limiting step for absorption from the gastrointestinal tract is a significantly slower dissolution rate. A common approach to improve the dissolution rate of poorly water-soluble drugs, and, therefore, improve oral bioavailability is by formation of a solid dispersion (Chiou and Riegelman, 1971; Serajuddin, 1999) with a water-soluble rate-enhancing polymer, such as polyethylene glycol. Typical methods for fabricating solid dispersions include solution methods (Sumnu, 1986; Mura et al., 1996; Doshi et al., 1997) and melt methods (Mura et al.,

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1996; Doshi et al., 1997; Mura et al., 1999; Yan et al., 2000), but these techniques are not readily scalable and have the disadvantages of solvent use and potential drug degradation at elevated temperatures. Broman et al. (2001) describe a novel method to fabricate solid dispersions utilizing compression moulding, but this technique also utilizes elevated temperature and a thermoplastic polymer.

Several researchers have developed methods to use hydroxypropyl methylcellulose (HPMC) as a dissolution rate-enhancing polymer (Kerc et al., 1997; Okimoto et al., 1997; Sugimoto et al., 1998; Usui et al., 1998; Iskandarsyah et al., 1999). However, use of HPMC in solid dispersions is complicated by its unique solution properties, non-thermoplastic nature, and charring at elevated temperature. There is a need in the pharmaceutical industry for an easily scalable method to combine poorly water-soluble drugs and dissolution rate-enhancing polymers without the use of solvent or heat addition. Therefore, the purpose of this study was to enhance the dissolution rate of poorly water-soluble drugs with HPMC using a readily scalable dry compaction process.

2. Materials and methods

HPMC USP Type 2208 (methoxyl content: 19–24%; hydroxypropyl content: 7–12%) with nominal viscosity for a 2% (w/v) aqueous solution of 3 mPa s (METHOCEL[2] Cellulose Ether K3LV Premium) was obtained from The Dow Chemical Company (Midland, MI). HPMC USP Type 2910 (methoxyl content: 28–30%; hydroxypropyl content: 7–12%) with nominal viscosity for a 2% (w/v) aqueous solution of 3 and 5 mPa s (METHOCEL Cellulose Ethers E3LV Premium and E5LV Premium, respectively) were also obtained from The Dow Chemical Company. An experimental sample of low-viscosity methylcellulose (MC) was prepared by subjecting a sample of METHOCEL Cellulose Ether A4M Premium to molecular weight reduction with anhydrous hydrochloric acid to reduce the viscosity to 5.5 mPa s (2% w/v aqueous solution). The model poorly soluble actives used were naproxen USP (Spectrum, Gardena, CA), nifedipine USP (Pharmrite, Stirling, NJ), and carbamazepine USP ('CBZ', Spectrum).

2.1. Sample preparation

2.1.1. Preparation of slugged powder mixtures

Physical mixtures of HPMC and one of the poorly water-soluble drugs (naproxen, nifedipine, and carbamazepine) at a 1:1 polymer:drug weight ratio were dry-blended. Slugs were compressed from the resulting physical mixtures on a Carver Press (Model C, Sterling Inc., Menomonee Falls, WI) with a 10 s dwell time. Round, flat-faced punches with 22-mm diameter were used. A compression force of 45 kN, corresponding to a compression pressure of 118 MPa was utilized for all slugs, and the range for slug weight was 500–600 mg. The resulting slugs were milled with a CoMil (Model 197S, Quadro Engineering, Waterloo, Ont., Canada) at 1450 rpm using a round-hole, grater-type screen and impeller to produce a free-flowing powder.

2.1.2. Preparation of roller compacted powder mixtures

Physical mixtures of HPMC and one of the poorly water-soluble drugs (naproxen, nifedipine, and carbamazepine) at a 1:1 polymer:drug weight ratio were dry-blended. Ribbons were formed on a roller compactor (Model TF-Mini, Vector Corporation, Marion, IA). Roller compactor operating conditions utilized a screw motor speed of 8.0 rpm (0.6 A) for naproxen and nifedipine, and 4.0 rpm (0.3 A) for carbamazepine. All preparations used a roll motor speed of 2.0 rpm (1.3 A) and a roll force of 3 tons. The ribbons were milled with a CoMil at 1000 rpm using a round-hole, grater-type screen and impeller to produce a free-flowing powder.

2.2. Drug dissolution

The USP dissolution apparatus (Distek Inc., North Brunswick, NJ) Type II (paddles) at rotation speed of 100 rpm was used for in vitro testing

[2] Trademark of The Dow Chemical Company.

of drug dissolution from the powder mixtures. An amount of powder equivalent to 100 mg of drug was added to the dissolution medium. The dissolution medium consisted of 900 ml of deionized water at 37.0 ± 0.5 °C. Samples were automatically withdrawn, filtered in-line, and assayed by ultraviolet absorbance (naproxen 272–274 nm, nifedipine 340–342 nm, carbamazepine 286–288 nm). The apparent solubility of each drug in the dissolution medium was also measured in a similar manner. An excess amount (100–500 mg) of the poorly soluble drug, as received, was placed into the dissolution medium and monitored by ultraviolet absorbance for 5 days.

2.3. Determination of dose distribution

2.3.1. Sieve analysis of mixtures

A sieve analysis was performed on a portion of each mixture and drug as received. An ATM Sonic Sifter (Model P, Milwaukee, WI) was used on sift/pulse mode for 5 min at amplitude 8. A sample (20–25 g) of each mixture was sieved through a stack of sieves comprised of the following sizes: No. 40 (425 μm), No. 60 (250 μm), No. 100 (150 μm), No. 200 (75 μm). The mass fraction of the total sample was determined having the following particle size ranges: <75, 75–150, 150–250, 250–425, and >425 μm.

2.3.2. HPLC analysis of mixtures for drug content

The drug content of each sieve cut from the sieve analysis as well as the composite sample (i.e. the unsieved sample) was determined by HPLC. The HPLC assay methods for naproxen, nifedipine, and carbamazepine were based on recommended methods presented in the USP; however, some modifications to these assays were developed to accommodate HPMC being present in the samples. The HPLC system consisted of a Hewlett Packard Control Module, Wavelength Detector, and Isocratic Pump (1100 series) with Hewlett Packard Auto Sampler (Model G1313A).

2.3.2.1. Naproxen HPLC assay. Mobile phase of 750 ml acetonitrile, 735 ml water, and 15 ml glacial acetic acid was used at room temperature. HPLC analysis was performed using ODS-120T column (Tosohaas), 4.6 mm × 25 cm, diameter of packing of 5 μm. Flow rate was 1.2 ml/min and absorbance was measured at 254 nm with UV detector.

2.3.2.2. Nifedipine HPLC assay. Mobile phase of 2.0 l water, 1.0 l acetonitrile, and 1.0 l methanol was used at room temperature. HPLC analysis was performed using ODS-120T column (Tosohaas), 4.6 mm × 25 cm, diameter of packing of 5 μm. Flow rate was 1.0 ml/min and absorbance was measured at 235 nm with UV detector.

2.3.2.3. Carbamazepine HPLC assay. Mobile phase of 1096 ml water, 822 ml methanol, and 82 ml methylene chloride was used at room temperature. HPLC analysis was performed using a WAT011797 column (Waters Corp.), 3.9 mm × 30 cm, diameter of packing of 15 μm. Flow rate was 2.0 ml/min and absorbance was measured at 230 nm with UV detector.

2.4. Solid state characterization

2.4.1. Differential scanning calorimetry

A TA Instruments differential scanning calorimeter (Model 2920) with a mechanical cooler and a standard cell was used to measure the thermal properties of the powder samples. Each sample was loaded into an open aluminum pan and placed into the differential scanning calorimetry (DSC) cell. The cell had a nitrogen purge flowing at approximately 40 cm^3/min. The cell and sample were held isothermally at -10 °C for 20 min to purge the headspace and sample with nitrogen before heating. The cell and sample were then heated to 250 °C at 10.00 °C/min while monitoring heat flow.

2.4.2. Powder X-ray diffraction

The samples were mounted on zero scatter background holders and analyzed using a Bruker D-8 automated diffractometer equipped with a position sensitive detector. Data was collected from 5 to 90° 2-theta, 0.0144°/step, 2 s/step with the Cobalt X-ray tube operating at 40 mA/40 kV.

3. Results and discussion

3.1. Use of HPMC to enhance dissolution of model drugs

The three model actives used in this study are poorly soluble in deionized water at 37 °C to varying degrees (Table 1). This was reflected in the dissolution studies conducted on the drugs as received. Naproxen as received had a relatively slow and variable dissolution profile (Fig. 1). The dissolution profile for nifedipine was slower and more consistent (Fig. 2). Dissolution for carbamazepine is shown in Fig. 3.

HPMC (K3LV Premium) was used to enhance the rate of dissolution for naproxen, nifedipine and carbamazepine. Three different means of combining HPMC and drug were utilized: dry-blending of drug and polymer to produce a simple physical mixture, and compacting the blends by either roller compaction or slugging with subsequent milling. Both the roller compaction and the slugging processes resulted in enhanced dissolution rate for the poorly water-soluble drugs compared to the drug as received and the corresponding physical mixture. The roller compaction and slugging methods produced comparable rate and extent of drug dissolution.

Table 1
Apparent solubility of the drugs in the dissolution medium—deionized water at 37 °C (mean, $n = 6$)

Drug	Measured apparent solubility (mg/l)	Apparent solubility as previously reported in the literature (mg/l)
Nifedipine	16	11.45[a]
Naproxen	45	50[b]
Carbamazepine	271	260[c]

[a] Distilled water (Sumnu, 1986).
[b] Bidistilled water, estimated from Figure 1 of Mura et al. (1999).
[c] Minimum physiologic solubility in the physiological pH range and temperature (Amidon et al., 1995).

3.2. Use of different HPMC types and MC to enhance dissolution of naproxen

Dissolution enhancement for the compaction process was comparable when different types of HPMC, specifically K3LV Premium, E3LV Premium, and E5LV Premium, were used (Fig. 4). These types of HPMC differ in the amount of methoxyl substitution and viscosity as a 2% aqueous solution. The experimental sample of low-viscosity MC was also effective in enhancing drug dissolution when used in the compaction process (data not shown).

3.3. Effects of the compaction process on drug distribution

Particle size distributions for the drugs as received were not similar (Fig. 5a). Fig. 5b–d combine the sieve analysis particle size distribution and the HPLC assays to show how the total drug dose was distributed among the particle size ranges. As expected, the drug dose distribution for physical mixtures (Fig. 5b) was essentially the same as for the respective drugs alone (Fig. 5a). As shown in Fig. 5c and d, after the roller compaction or slugging compaction process, the dose distribution profiles for all three poorly water-soluble drugs were similar to one another, despite the significant differences in particle size distribution of the respective drugs as received (Fig. 5a). The roller compaction process incorporated more of the total drug dose into particles of the largest size (>425 μm) than did the slugging compaction process. This may be due to a more efficient granulating process for roller compaction, differences in compression pressure, or milling conditions. However, despite the differences between the roller compacted and slugged dose distributions (Fig. 5c vs. d), drug dissolution for the composite samples was comparable for either compaction technique (Figs. 1–3).

3.4. Mechanism of dissolution enhancement

The mechanism for how the compaction/milling process yields enhanced dissolution properties is believed to be a microenvironment surfactant

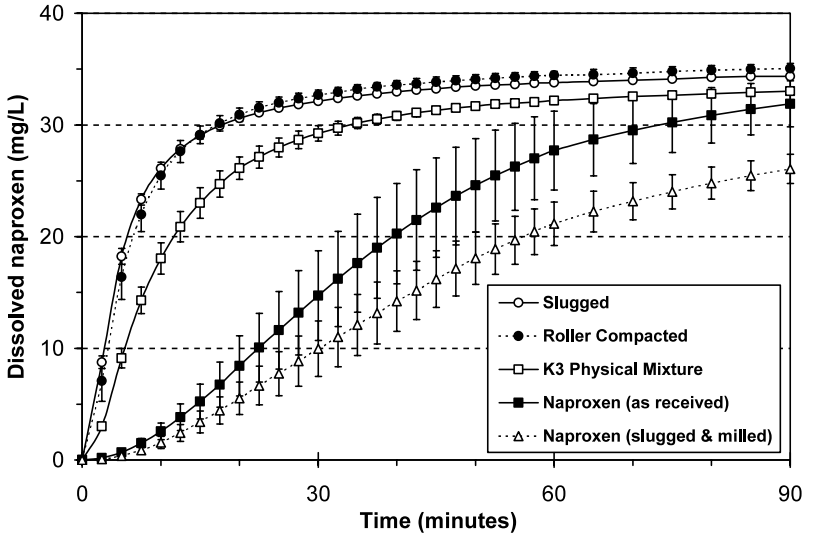

Fig. 1. Naproxen dissolution in deionized water at 37 °C for naproxen as received, physical mixture, and slugged and roller compacted powder (mean ± S.D., $n = 3$). Dissolution for naproxen slugged and milled without the presence of HPMC is also shown.

effect whereby HPMC dissolution creates a local surfactant concentration in the boundary layer surrounding the drug particles, providing a lower-energy pathway for drug dissolution. The compaction processes are believed to be particularly effective at enhancing the rate of drug dissolution because the drug particles are maintained in direct contact with the HPMC particles during drug dissolution, in contrast with a physical mixture where the drug and HPMC particles may quickly disperse and be separated in the dissolution medium.

Evidence that HPMC may act as a surfactant to facilitate drug dissolution is found in Figs. 1 and 3,

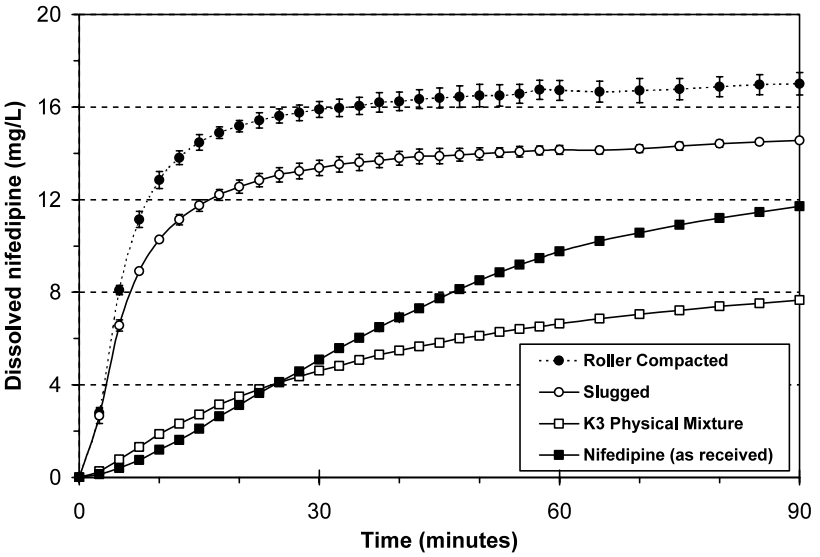

Fig. 2. Nifedipine dissolution in deionized water at 37 °C for nifedipine as received, physical mixture, and slugged and roller compacted powder (mean ± S.D., $n = 3$).

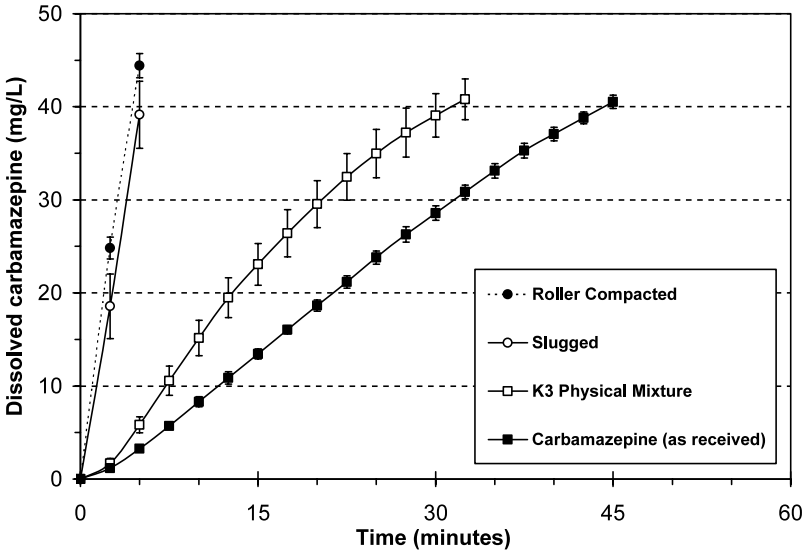

Fig. 3. Carbamazepine dissolution in deionized water at 37 °C for carbamazepine as received, physical mixture, and slugged and roller compacted powder. The curves are truncated at about 40 mg/l due to detection limits (mean ± S.D., $n = 3$).

and Fig. 4 where dissolved HPMC in the bulk medium resulted in faster drug dissolution for physical mixtures compared to the drug alone. It was also demonstrated that HPMC presence is critical to the dissolution enhancement mechanism. Samples of the drugs alone subjected to the same slugging and milling procedure did not exhibit faster drug dissolution. Rather, slugged and milled naproxen alone had a dissolution rate that was slower than the drug as received (Fig. 1). Equivalent results were obtained for nifedipine and carbamazepine as well (data not shown).

The compaction and milling procedures did not alter the bulk thermal properties or the X-ray diffractograms for the drugs (Figs. 6 and 7). Differences were observed between the en-

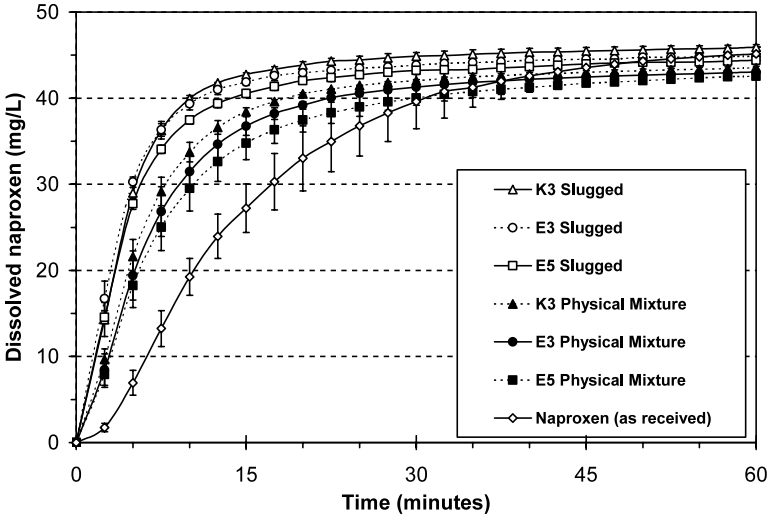

Fig. 4. Naproxen dissolution in deionized water at 37 °C using different types of HPMC—K3, E3, and E5 (mean ± S.D., $n = 3$).

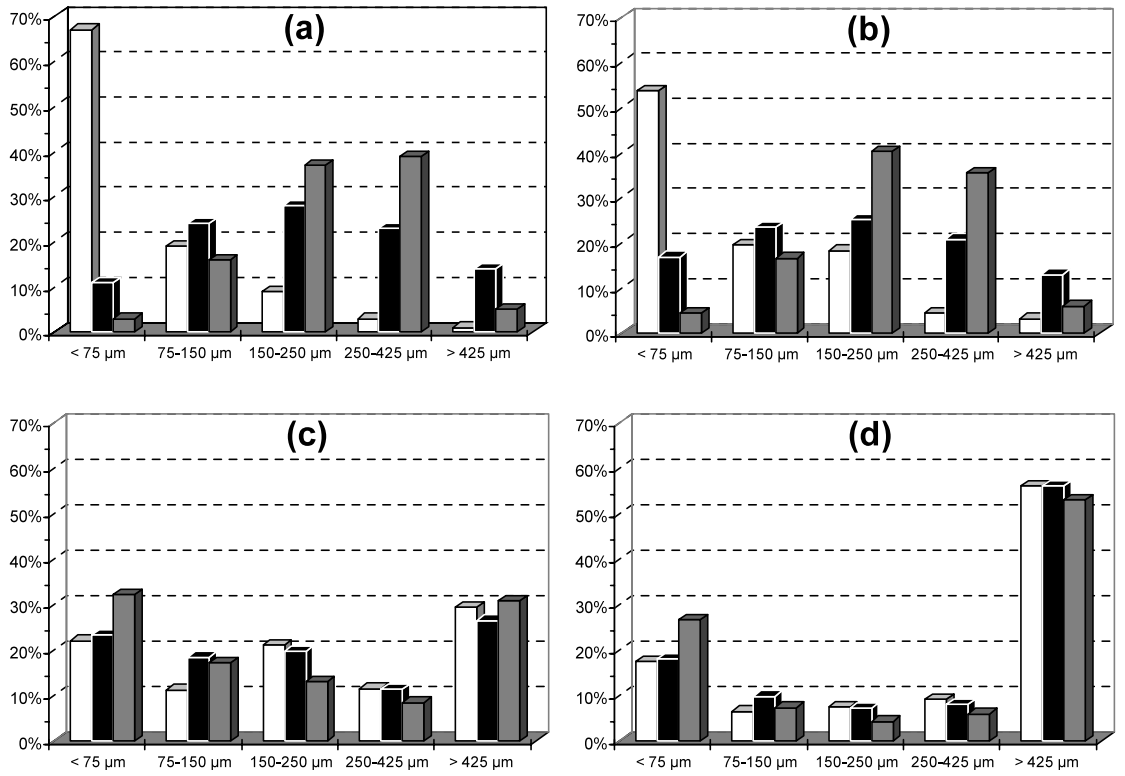

Fig. 5. Dose distribution of naproxen (□), nifedipine (■), and carbamazepine (■). (a) As received; (b) physical mixture; (c) slugged; (d) roller compacted.

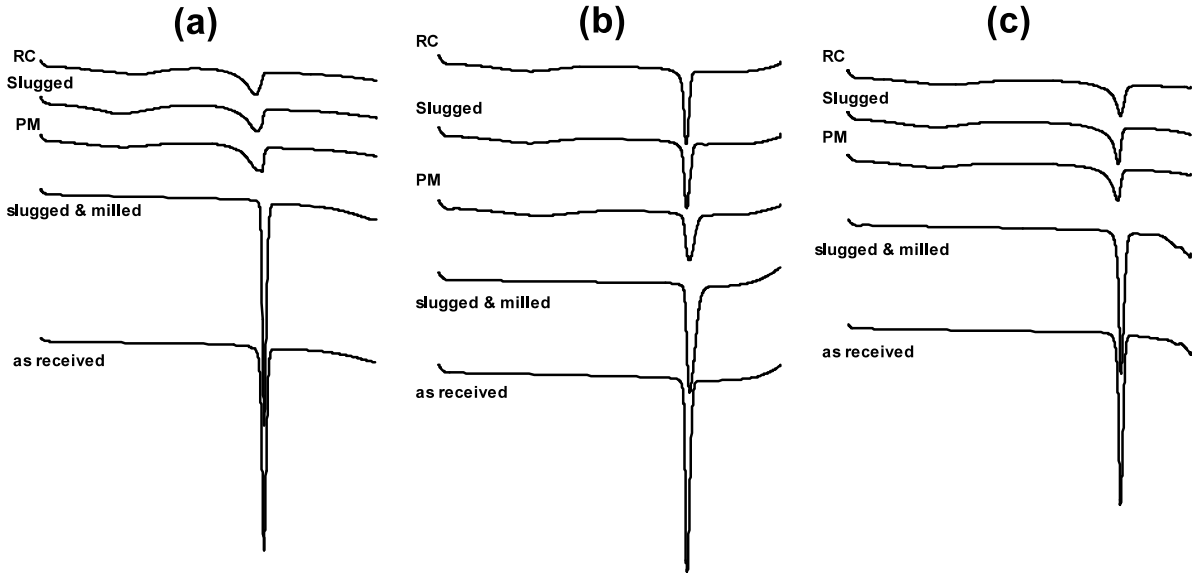

Fig. 6. DSC results for (a) naproxen, (b) nifedipine, and (c) carbamazepine. Scans are shown for the drug as received, the drug slugged and milled alone (slugged and milled), an HPMC physical mixture (PM), the slugging procedure (slugged), and the roller compaction procedure (RC). The top three curves represent an HPMC/drug mixture while the bottom two curves represent the drug alone.

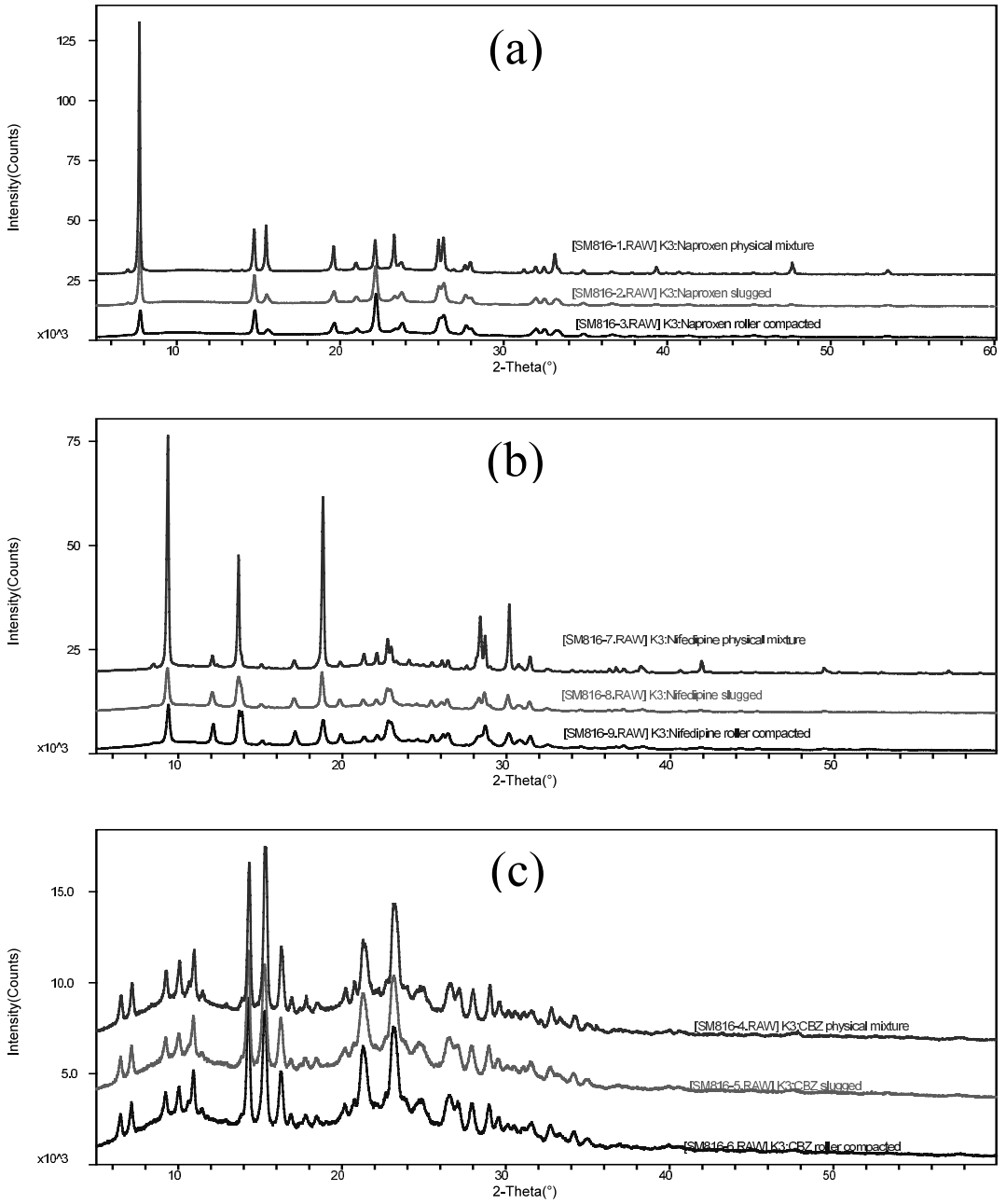

Fig. 7. Powder X-ray diffractograms for (a) naproxen, (b) nifedipine, and (c) carbamazepine mixtures.

dotherms for the drug-only powders compared to the HPMC/drug mixtures. However, in each case the endotherm was unchanged by the compaction and milling processes (Fig. 6—'as received' vs. 'slugged and milled'; 'PM' vs. 'slugged' and 'RC'). Aside from a few changes in peak intensity corresponding to removal of the preferred crystal orientation in the physical mixtures upon granulation, the compaction processes caused no changes in diffraction patterns (Fig. 7). Peak broadening

was not observed in the diffractograms, indicating that compression and milling of the drug crystals did not produce an appreciable number of small drug crystals less than ~ 0.2 μm in dimension (Klug and Alexander, 1954) via brittle fracture.

4. Conclusions

A readily scalable compaction process requiring no solvent and no heat addition was effective in enhancing drug dissolution of three poorly water-soluble drugs. Compacting poorly water-soluble drug particles with low molecular weight cellulose ether (HPMC or MC) particles resulted in a granular powder having enhanced drug dissolution properties. Drug dissolution rates were comparable for roller compacted and slugged powders, suggesting that differences in compaction processes were not critical in dictating drug dissolution rate. The mechanism is believed to be a microenvironment HPMC surfactant effect facilitated by keeping the HPMC and drug particles in close proximity during drug dissolution.

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