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Research Article

Low-Viscosity Hydroxypropylcellulose (HPC) Grades SL and SSL: Versatile Pharmaceutical Polymers for Dissolution Enhancement, Controlled Release, and Pharmaceutical Processing

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Abstract. Hydroxypropylcellulose (HPC)-SL and -SSL, low-viscosity hydroxypropylcellulose polymers, are versatile pharmaceutical excipients. The utility of HPC polymers was assessed for both dissolution enhancement and sustained release of pharmaceutical drugs using various processing techniques. The BCS class II drugs carbamazepine (CBZ), hydrochlorthiazide, and phenytoin (PHT) were hot melt mixed (HMM) with various polymers. PHT formulations produced by solvent evaporation (SE) and ball milling (BM) were prepared using HPC-SSL. HMM formulations of BCS class I chlorpheniramine maleate (CPM) were prepared using HPC-SL and -SSL. These solid dispersions (SDs) manufactured using different processes were evaluated for amorphous transformation and dissolution characteristics. Drug degradation because of HMM processing was also assessed. Amorphous conversion using HMM could be achieved only for relatively low-melting CBZ and CPM. SE and BM did not produce amorphous SDs of PHT using HPC-SSL. Chemical stability of all the drugs was maintained using HPC during the HMM process. Dissolution enhancement was observed in HPC-based HMMs and compared well to other polymers. The dissolution enhancement of PHT was in the order of SE>BM>HMM>physical mixtures, as compared to the pure drug, perhaps due to more intimate mixing that occurred during SE and BM than in HMM. Dissolution of CPM could be significantly sustained in simulated gastric and intestinal fluids using HPC polymers. These studies revealed that low-viscosity HPC-SL and -SSL can be employed to produce chemically stable SDs of poorly as well as highly water-soluble drugs using various pharmaceutical processes in order to control drug dissolution.

KEY WORDS: controlled release formulations; hydroxypropylcellulose; melt extrusion; solid dispersion.

INTRODUCTION

The biopharmaceutical classification system (BCS) categorizes active pharmaceutical ingredients (APIs) into four classes based upon their aqueous solubility and gastrointestinal permeability (1). According to the BCS, class II compounds exhibit low solubility and high permeability due to their crystalline hydrophobic characteristics which result in poor bioavailability after oral administration (2). BCS class I drugs are both highly soluble and permeable, and often require frequent administration due to their rapid elimination in order to maintain therapeutic blood levels, which may lead to poor patient compliance (3). Over 40% of the new chemical entities that are being discovered today by high-throughput screening and combinatorial chemistry fall into the BCS class II category (4). Various techniques, such as particle size reduction, crystal habit modification, polymorphism, complexation, solubilization, solid dispersions (SDs) in carriers, and prodrug and salt formation are employed in order to improve the aqueous solubility of class II drugs (1). The solid dispersion of such drugs into polymeric carriers using hot melt and solvent methods has gained much attention in the pharmaceutical industry (5). Hot melt extrusion (HME) is an attractive technology for manufacturing SDs that involves continuous mixing and extrusion of materials comprising drug(s), thermoplastic polymers, and other components such as plasticizers and antioxidants at elevated temperatures through a die in the shape of cylinders or films (6). Such high shear mixing at relatively higher temperatures produces SDs characterized by amorphous conversion of the formerly crystalline drug and the development of drug–polymer interactions, which may improve aqueous solubility of a drug. Also, HME can be used as a continuous process without the need of solvents and subsequent drying steps and may be used along with other excipients such as plasticizers, surfactants, and antioxidants (7,8). In addition to solubility enhancement, HME can also be used to sustain the release rate of class I APIs by dispersing these highly water-soluble compounds into high viscosity thermoplastic polymer matrices, thereby sustaining their release rate in the gastrointestinal tract (9,10).

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Although HME exhibits numerous advantages and applications, its limitations include low amorphous conversion efficiency and poor dispersion of higher melting drugs, as well as potential thermal degradation of API's and polymers at operating temperatures. In many cases, plasticizers are required to reduce the polymer glass transition temperature (Tg) and melt viscosity by increasing the free volume between polymer chains in order to perform HME at an acceptable temperature (11,12). However, their inclusion may lead to drug–polymer immiscibility and re-crystallization (13,14). Certain low Tg polymers may be used to manufacture SDs of high melting drugs without the use of plasticizers (15). Hydroxypropylcellulose (HPC) is a semi-crystalline polymer with amorphous domains of very low Tg along with the crystalline domains. Thus, HPC depicts higher molecular mobility and plasticity due to a high degree of amorphous content with a low Tg (16). HPC may cause melting point (Tm) depression of high melting drugs, much like other polymers such as PVP-VA and HPMC that are used to produce SDs at relatively lower operating temperatures using HME (17). The amorphous conversion of poorly water-soluble drugs as well as size reduction of their crystalline form along with intimate mixing and dispersion in hydrophilic polymers can also be achieved using solvent evaporation or particle size reduction techniques in order to improve their solubility. HPC is a cellulose ether in which some of the hydroxyl groups of the repeating glucose units are substituted with $-OCH_2CH(OH)CH_3$ groups using propylene oxide (18). Therefore, HPC depicts organic as well as water solubility and hence is suitable for solvent methods to manufacture SDs (19). In addition, it also has lower critical solution temperature of 45°C due to the presence of both hydrophilic and hydrophobic groups and forms liquid crystals and many other mesophases in water, depending upon concentration (20–22). Such liquid crystalline phases may form gel-like layers associated with hydrated HPC formulation to control the release of highly water-soluble drugs (23). The degree of hydroxypropyl substitution can be altered in order to tailor the viscosity of the polymer, used in turn for sustained release of the APIs. HPC's may thus be attractive excipients for many pharmaceutical applications.

In this investigation, the utility of low-viscosity HPC-SL and -SSL polymers has been assessed for the first time as HME excipients as compared to other polymers for dissolution enhancement of API's. The physicochemical properties of the drugs and the polymers that are used in this investigation are shown in Tables I and II, respectively. Three BCS class II drugs with high Tm and different chemical properties were evaluated. Carbamazepine (CBZ) is a neutral carbamate drug, phenytoin (PHT) a hydantoin acid, and hydrochlorothiazide (HCTZ) a weak aromatic amine base. In this study, the processability and dissolution enhancement efficiency of SDs manufactured by hot melt mixing (HMM) using these drugs as model API's with the non-ionic HPC-SL and -SSL polymers have been compared to analogous HMMs formulated using other polymers with various polymeric backbones and functional groups. Specifically, those polymers compared to the neutral, cellulosic HPC polymers included Eudragit EPO (cationic tertiary amine), Eudragit L-100-55 and HPMCAS-LF (anionic polycarboxylates), and PVP-VA 64 (a non-ionic, amide polymer). The Tm of the API's and Tg of the polymers might be expected to strongly influence the amorphous conversion of API's at suitable HMM processing temperatures, thereby playing an important role in solid dispersion formation and dissolution characteristics. In order to further evaluate the utility of low-viscosity HPC as a versatile pharmaceutical excipient, HPC-SSL has also been evaluated using solvent evaporation and ball milling in order to determine the effect of HPC-SSL upon dissolution enhancement, if any, of the very high melting, water-insoluble drug PHT. Further evaluating the formulation characteristics of low-viscosity grades of HPC, both HPC-SL and -SSL were melt mixed with the highly soluble, BCS class I compound chlorpheniramine maleate (CPM) in order to study the sustained release applications of low-viscosity HPC polymers using HMM technology.

MATERIALS AND METHODS

Materials

CBZ, PHT, and CPM were purchased from Sigma Aldrich (St. Louis, Missouri, USA). HCTZ was purchased from Merck Sharp and Dohme Research Lab (West Point, Pennsylvania, USA). The cellulosic polymers HPC-SL and HPC-SSL were obtained from Nisso America, Inc. (New York, New York, USA). HPMCAS-LF manufactured by Shin-Etsu (Niigata, Japan) was obtained from Biddle Sawyer (New York, New York, USA). Eudragit EPO and Eudragit L-100-55 were obtained from Evonik Degussa (New Jersey, USA). Kollidon VA-64 was obtained from BASF (New Jersey, USA). All other chemicals and reagents were purchased from Fisher Scientific and were of analytical grade.

Methods

Preparation of Physical Mixtures

The drugs were gently mixed with the polymers using a glass mortar and pestle for 5 min at a 25:75 drug–polymer *w*/*w* ratio to prepare 45 g each of the corresponding physical

Table I. Physicochemical Properties of the API's

	Physicochemical properties				
Drug	BCS class	Ionic nature	pK_a	Molecular weight	Tm (°C)
CBZ	II	Neutral	N/A	236.27	190
HCTZ	II	Weakly basic	7.9	297.74	274
PHT	II	Weakly acidic	8.3	252.23	295
CPM	I	Salt of a weak base	9.2	390.87	132

Table II. Physicochemical Properties of the Polymers

Polymer	Physicochemical properties				
	Backbone	Ionic nature	Ionic group	Molecular weight	Tg/Tm[a] (°C)
HPC-SL	Cellulosic	Non-ionic	N/A	100,000	−25~0/180~220
HPC-SSL	Cellulosic	Non-ionic	N/A	40,000	−25~0/180~220
HPMCAS-LF	Cellulosic	Anionic	–COOH	180,000	120/NA
PVP-VA	Vinyl	Non-ionic	N/A	45,000–70,000	107/NA
Eudragit L-100-55	Methacrylic	Anionic	–COOH	250,000	110/NA
Eudragit EPO	Methacrylic	Cationic	$–NR_3$	150,000	50/NA

[a] Tm is applicable for semi-crystalline polymers

mixtures (PMs). These PMs were then transferred to amber colored glass bottles for homogeneous mixing in a Turbula blender (Willy A Bachofen, Basel, Switzerland) for 15 min. The blended PMs were then compacted using Carver press at 4,000-psi pressure and a dwell time of 30 s. These compacted PMs were milled using a twin-blade rotary mill and then sieved between US mesh nos. 40 and 60 (250–420 μm). This size fraction was stored in a desiccator and used in subsequent studies. All the characterization and dissolution studies were performed within a period of 1 week after the physical mixing or melt mix formulation of each drug.

Hot Melt Mixing

A three-piece hot melt mixer with roller blades (C. W. Brabender Instruments, Inc., Hackensack, New Jersey, USA) was used to manufacture the hot melt mixed formulations (HMMs). About 40 g of the corresponding PM was fed in the hot melt mixer and mixed at 150 rpm for 5 min. The melt mixing temperatures were selected in order to facilitate adequate mixing of the drugs and polymers and to reduce the torque and mechanical strain in the mixer by softening the polymers, thereby leading to transparent, amorphous SDs. Melt mix temperatures did not exceed 180°C, even for very high melting drugs, in order to prevent thermal degradation of drugs and polymers. Likewise, this demonstrates the important processing characteristic that melt mixing of polymer–drug combinations may lead to the formation of amorphous drug–polymer dispersions without need of processing at or near the melting temperature of the drug. For instance, the PMs of moderately high melting drug CBZ were mixed at 150°C, and those of very high melting PHT and HCTZ were mixed at 180°C. Hot melt mixing of PMs of low-melting CPM was performed at 130°C, primarily to achieve adequate polymer softening and mixing and facilitate the mechanical processing of CPM with an HPC polymer. The resulting HMM products were milled using a twin-blade rotary mill and the size fractions sieved between US mesh nos. 40 and 60 (250–420 μm) were stored in a desiccator and used in subsequent studies. The characterization and dissolution studies were performed within 1 week after formulation and processing for each drug.

Ball Milling

Ten grams of the PM comprising PHT:HPC-SSL (25:75) was loaded into the bowl of a planetary ball mill (Retsch PM 100, Newtown, Pennsylvania, USA). The mill was then operated at 400 rpm for 30 min using 50 milling balls of 10-mm diameter. The ball milled product (BM) was then compacted using a Carver press at 4,000-psi pressure and a dwell time of 30 s. The compacted BM was milled using a twin-blade rotary mill and then sieved between US mesh nos. 40 and 60 (250–420 μm). This size fraction was stored in a desiccator and then used in subsequent studies. The characterization and dissolution studies were performed within 1 week after formulation and processing for each drug.

Solvent Evaporation

Ten grams of the PM comprising PHT:HPC-SSL (25:75) was dissolved in 120 ml methanol. This solution was transferred to a 500-ml round-bottom flask and the methanol was rapidly evaporated *in vacuo* using a rotary evaporator (Heidolph Collegiate Brinkmann, Webco) at 60–70°C and 100–120 rpm for 30 min. The resulting solid dispersion was further dried in a vacuum oven at 40°C for 12 h, removed from the flask, and then milled using a twin-blade rotary mill. The milled solvent evaporated product (SE) was sieved between US mesh nos. 40 and 60 (250–420 μm) and this size fraction was stored in desicattor and used in subsequent studies. The characterization and dissolution studies were performed within 1 week after formulation and processing for each drug.

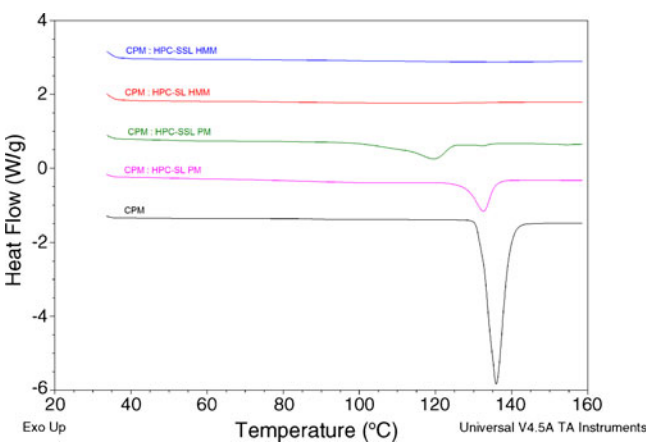

Fig. 1. First heating cycle DSC plots of CPM, its PMs, and HMMs formulated with HPC-SL and HPC-SSL

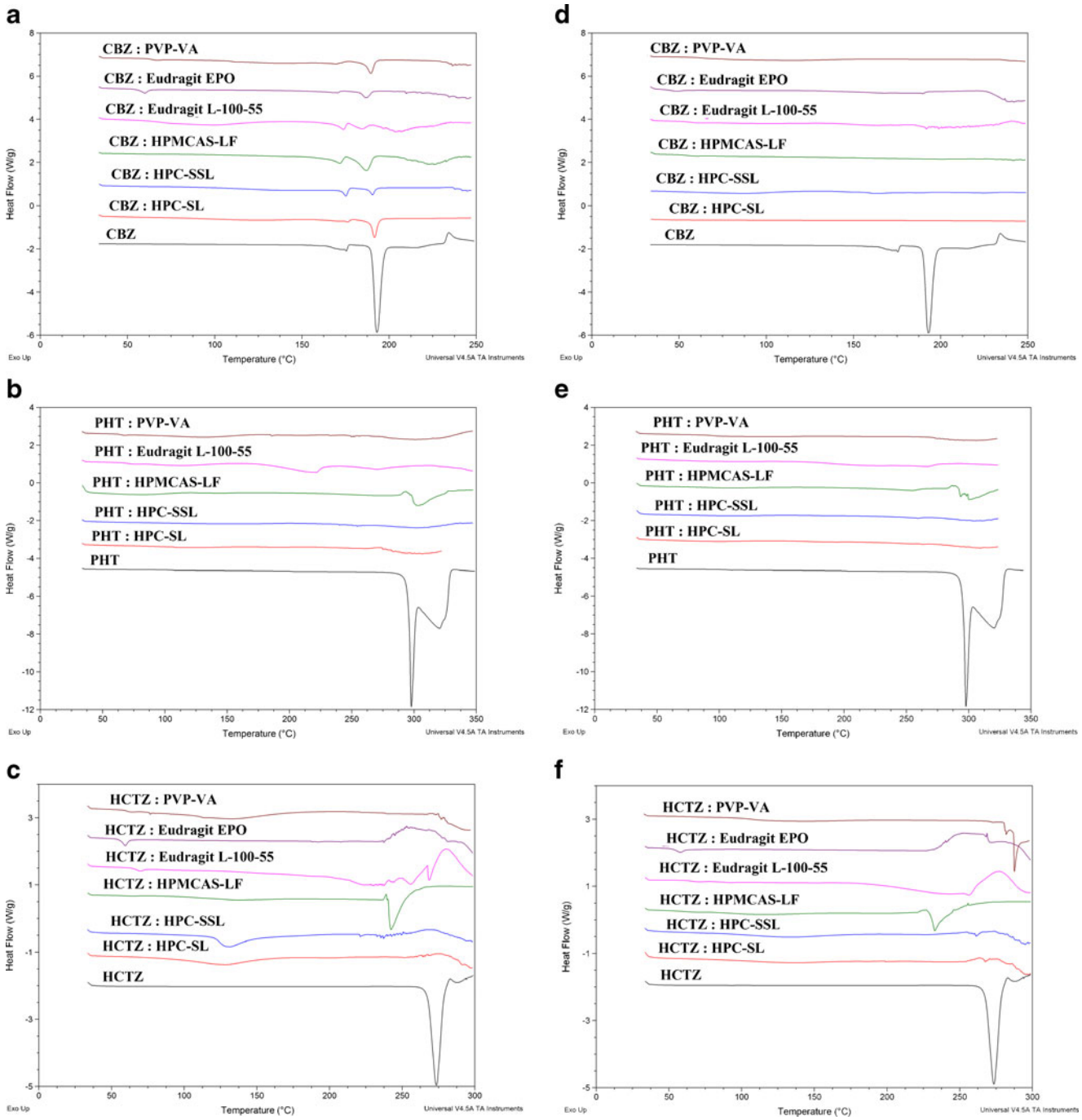

Fig. 2. First heating cycle DSC plots of PMs of **a** CBZ, **b** PHT, and **c** HCTZ; and HMMs of **d** CBZ, **e** PHT, and **f** HCTZ formulated with various polymers

Differential Scanning Calorimetry

Samples (5–7 mg) of each material were hermetically sealed in aluminum pans and subjected to heat–cool–heat cycling using a Q differential scanning calorimetry (DSC; TA Instruments, New Castle, Delaware, USA). The heating rate was 10°C/min and the cooling rate was 50°C/min. The DSC plots were interpreted using TA Universal Analysis software.

Polarized Light Microscopy

Samples were deposed on glass microscope slides using mineral oil and covered with cover slips. The slides were then observed with ×10 magnification at the highest intensity of light using a polarized light microscope (Amscope, Irvine, California, USA) equipped with a Uranus CMOS camera. The images were captured using Toup View software.

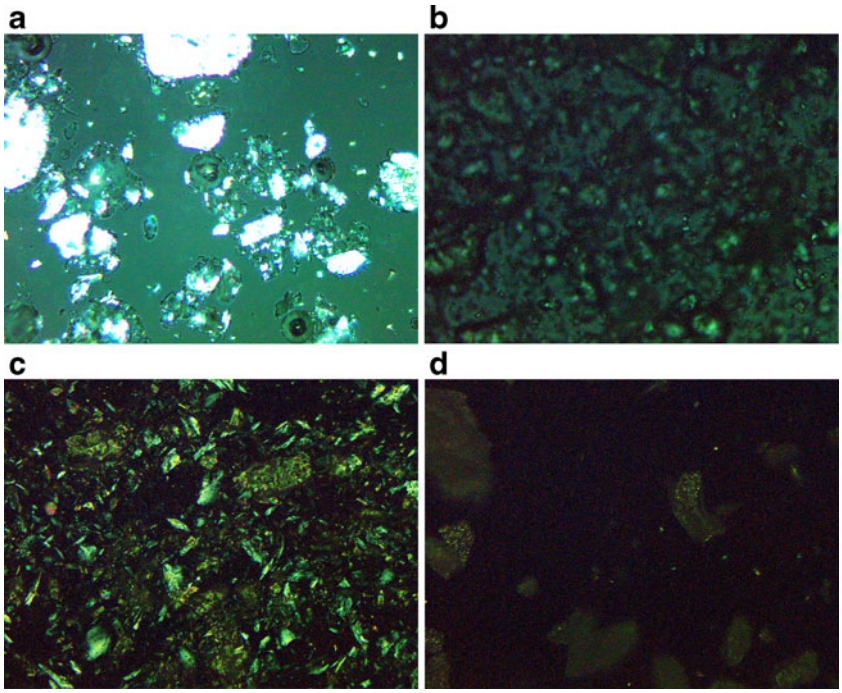

Fig. 3. PLM images of **a** CPM: HPC-SL PM, **b** CPM: HPC-SL HMM, **c** CBZ: HPC-SSL PM, and **d** CBZ: HPC-SSL HMM

HPLC Analysis

HPLC analysis of the HMM samples was performed using a LaChrom Elite system (Hitachi High-Tech) with an Agilent Zorbax Eclipse XDB-C18 (4.6×250 mm) column for all the drugs. Acetonitrile and water in the ratio of 30:70 *v/v* was used as the mobile phase for CBZ, PHT, and HCTZ. A mobile phase (pH 7.9) comprising water, acetonitrile, and triethylamine in the ratio of 64.9:32.7:2.4 by volume was used for CPM. The flow rate was 1 ml/min for all drugs and UV detection was employed at 220, 220, 271, and 265 nm for CBZ, PHT, HCTZ, and CPM, respectively. The retention times for CBZ, PHT, HCTZ, and CPM were 14.5, 17.1, 4.2, and 4.6 min, respectively. Drug concentrations in the HMM SD samples were determined based upon linear concentration *versus* area under curve plots generated for standard concentrations between 1 and 50 μg/ml and the theoretical concentration of the assayed samples was well within this linear range, typically 15 μg/ml.

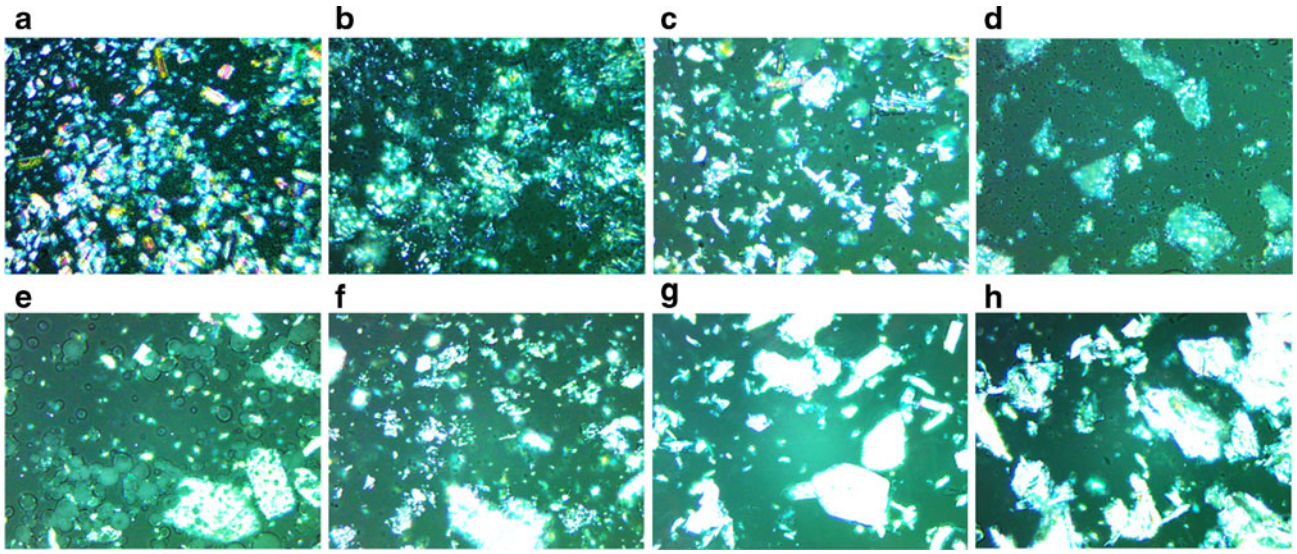

Fig. 4. PLM images of **a** PHT: Eudragit EPO PM and **b** PHT: Eudragit EPO HMM; **c** PHT: HPMCAS-LF PM and **d** PHT: HPMCAS-LF HMM; **e** HCTZ: Eudragit L-100-55 PM and **f** HCTZ: Eudragit L-100-55 HMM; **g** HCTZ: PVP-VA PM and **h** HCTZ: PVP-VA HMM

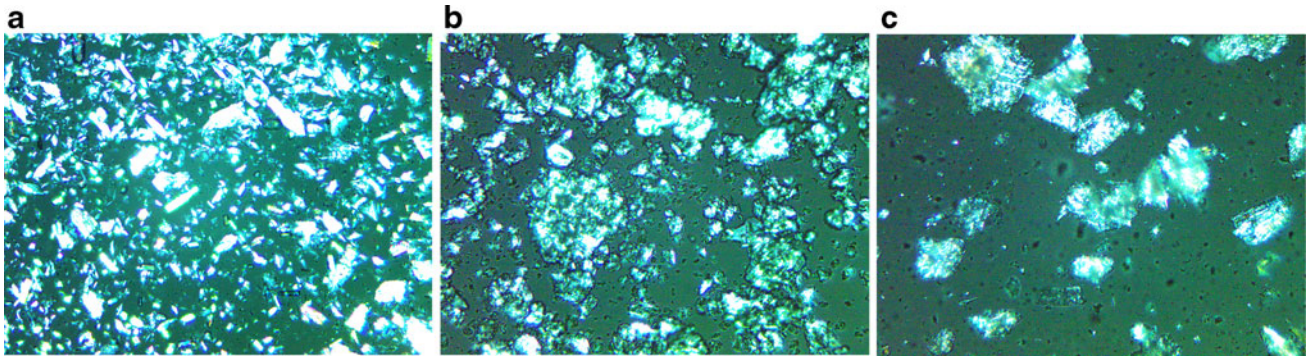

Fig. 5. PLM images of PHT: HPC-SSL **a** PM, **b** BM, and **c** SE formulations

Preparation of Capsule and Tablet Formulations for Dissolution Studies

The formulations obtained after PM, HMM, BM, and SE were either manually loaded into capsules or compressed into tablets as explained below. Aliquot parts of the milled formulations (250–420 μm) of CBZ, PHT, and HCTZ, each equivalent to 25 mg of the active drug, were loaded into size 0 gelatin capsules with sinkers to study their dissolution characteristics, whereas CPM formulations prepared with the HPC polymers for controlled release were compressed into tablets containing 62.5 mg equivalent of the active using a Stokes F-Press with 8-mm round tooling to evaluate drug release.

Dissolution Studies

Dissolution studies were carried out using a USP dissolution apparatus type II (LID-8D, Vanguard Pharmaceutical Machinery Inc., Texas, USA). The dissolution experiments were performed at 37±0.5°C and 50 rpm using 900 ml 50 mM phosphate buffer (pH6.8) as the dissolution medium. For formulations containing the basic, tertiary amine polymer Eudragit EPO, 0.1 N HCl was used as the dissolution medium. In all cases, serial dissolution samples were collected and filtered using 0.22-μm syringe filters (MCE membrane). These samples were then transferred to Costar clear 96-well plates and analyzed using a UV detector (SpectraMax M2, Molecular Devices, Pennsylvania, USA). Drug concentrations in the dissolution samples were determined based upon linear concentration–absorbance plots generated at 285, 250, 271, and 265 nm for CBZ, PHT, HCTZ, and CPM, respectively (24–27).

Table III. Percent of Theoretical Drug Remaining in Each Formulation After HMM Processing, as Determined by HPLC (Data Represent the Average of Two Independent HPLC-Assayed Samples)

	Percentage of API remaining			
Polymer	CBZ	HCTZ	PHT	CPM
HPC-SL	97.07	95.36	99.42	100.50
HPC-SSL	98.77	95.34	100.07	100.14
HPMCAS-LF	78.66	102.44	96.57	N/A
PVP-VA	104.95	95.80	100.19	N/A
Eudragit L-100-55	35.18	94.02	104.00	N/A
Eudragit EPO	101.33	54.63	97.03	N/A

RESULTS AND DISCUSSION

Differential Scanning Calorimetry

As shown in Fig. 1, melting point depression of CPM was observed in its PMs formulated with HPC-SL and HPC-SSL, suggesting CPM–HPC interaction. Indeed, the melting endotherm of CPM was not detectable by DSC in corresponding HMMs, suggesting conversion of this crystalline drug salt into an amorphous solid dispersion in HPC by HMM. Although melting point depression was not observed in CBZ PMs (Fig. 2a), CBZ melting endotherms were not detected in CBZ HMMs formulated using any of the polymers (Fig. 2d), suggesting facile amorphous conversion of this drug by melt mixing in chemically diverse polymers. The DSC plots of PMs (Fig. 2b) and HMMs (Fig. 2e) of the very high melting drug PHT (>290°C) did not exhibit any significant difference near the melting endotherm. This reveals the presence of crystalline drug after HMM, irrespective of the chemical nature of the polymer employed. This likely reflects the strong crystalline habit of this high melting point drug, as well as possible degradation of the polymers at high temperatures, which may have compromised their drug solubilizing capacity. As shown in Fig. 2c, f, polymer degradation during DSC could have occurred near the relatively high HCTZ melting point

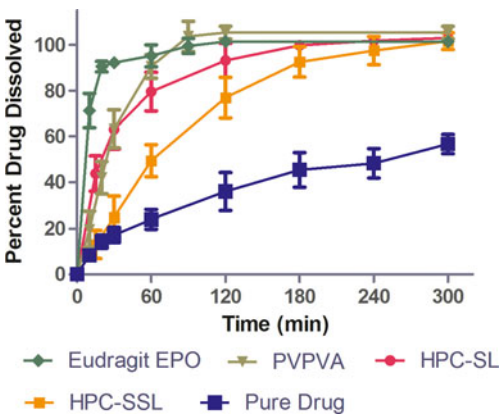

Fig. 6. Dissolution profiles of milled HMMs of CBZ using various polymers (as shown in Table I, degradation of CBZ was detected in HMMs with the anionic polymers HPMCAS-LF and Eudragit L-100-55. Their dissolution profiles are not included)

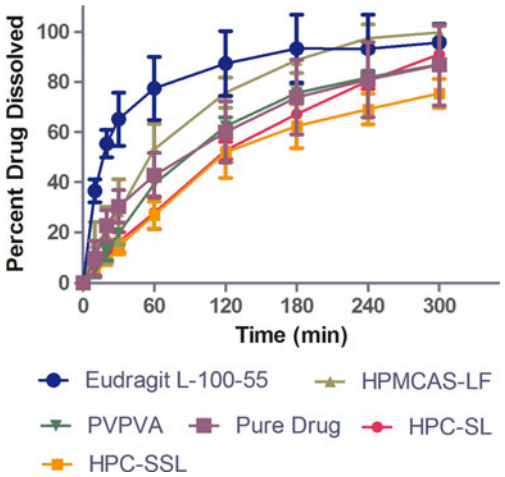

Fig. 7. Dissolution profiles of milled HMMs of HCTZ using various polymers (as shown in Table I, degradation of HCTZ was detected in HMMs containing the basic polymer Eudragit EPO. Its dissolution profile is not included)

(>250°C). Notably, the melting point of HCTZ was depressed by the cellulosic polymers HPC-SL, HPC-SSL, and HPMCAS-LF, with the greatest melting point depression detected using the HPC polymers. This melting point depression property of high melting API's with low glass transition HPC polymers might be advantageous for processing solid dispersions using hot melt methods at lower operating temperatures, even in cases where true amorphous solid dispersions are not obtained, in order to prevent drug and polymer degradation. In summary, amorphous conversion of CPM and CBZ occurred during the HMM process and could be verified using DSC experiments, but those of very high melting HCTZ and PHT could not be identified by DSC, although melting point depression of HCTZ was noted when cellulosic polymers such as HPC were employed as carriers. Subsequent thermal analysis of melt mixed materials after 2 months of storage at room temperature did not reveal any significant differences in their DSC thermograms.

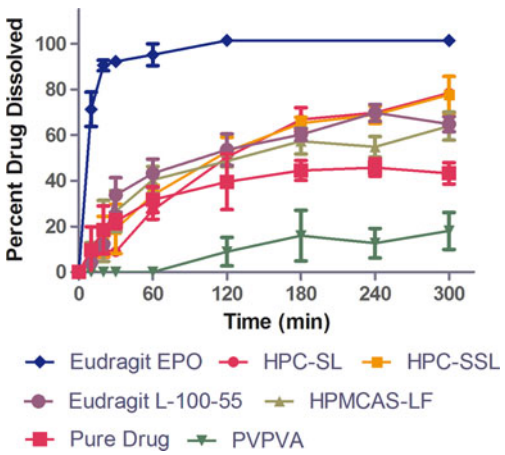

Fig. 8. Dissolution profiles of milled HMMs of PHT using various polymers

Polarized Light Microscopy

Polarized light microscopy (PLM) evaluation of CPM and CBZ correlated well with the DSC analysis. The birefringence of crystalline drug observed in the PLM images of PMs was not detected in the HMMs for CPM and CBZ melt mixed with HPC polymers (Fig. 3). Similar results were observed for CBZ with all other polymers, confirming amorphous conversion of CBZ-polymer HMM mixtures. However, significant birefringence was observed in the PLM images of the HMMs of PHT and HCTZ as compared to their corresponding PMs in all of the polymer systems tested (Fig. 4). Further, amorphous conversion of PHT with HPC-SSL could not be achieved using either ball milling or solvent evaporation, with significant birefringence detected in their PLM images as well (Fig. 5). As confirmed by PLM, amorphous solid dispersions of CPM and CBZ could be produced by HMM, while crystalline dispersions of HCTZ and PHT were produced using the HMM process. Solvent evaporation and ball milling also failed to produce amorphous solid dispersions of PHT when using HPC-SSL as the carrier.

HPLC Analysis

As shown in Table II, HPLC assays revealed that the theoretical percent recovery of drugs formulated with PVP-VA and both grades of HPC was between 95% and 105% of the theoretical concentration, suggesting that the drugs remained stable after HMM using these polymers. In contrast, significant degradation of CBZ occurred during the HMM process when formulated with the acidic carboxylated polymers HPMCAS-LF and Eudragit L-100-55, with only about 79% and 35% drug remaining, respectively. This might be attributed to acid-catalyzed or oxidative hydrolysis of CBZ in the presence of these polymers, as acid-catalyzed and oxidative hydrolysis of CBZ has been reported (28). Similarly, when formulated with the basic polymer Eudragit EPO, only about 55% of theoretical HCTZ remained in this HMM formulation, suggested base-catalyzed degradation, a phenomenon also reported in the literature (29). In contrast, no degradation was detected in the HMM products of any of the APIs when using the non-ionic polymers HPC and PVP-VA, suggesting a role for these polymers when acid- and base-labile drugs are formulated using HMM (Table III).

Dissolution Studies

The dissolution characteristics of all of the capsule formulations of the BCS class II APIs (CBZ, PHT, and HCTZ) studied here was investigated in 50 mM phosphate buffer, pH 6.8. For capsule formulations containing the Eudragit EPO, 0.1 N HCl was used as the dissolution medium in order to adequately hydrate and swell this basic polymer. Tablet formulations of the highly soluble, BCS class I drug CPM formulated using HPC polymers were investigated in both 50 mM phosphate buffer, pH 6.8 and in 0.1 N HCl in order to determine the effects of low-viscosity HPC on CPM release from compressed HMM tablets.

The dissolution rate and extent of the neutral carbamate drug CBZ was significantly improved over 5 h when

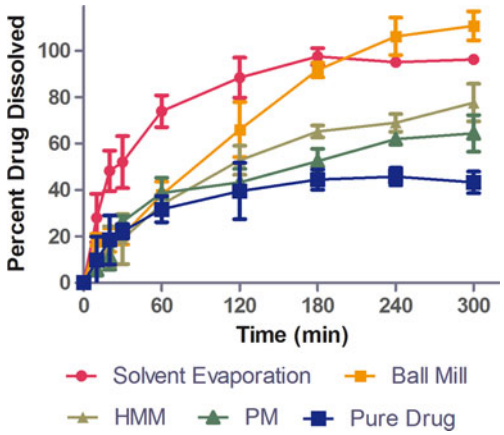

Fig. 9. Dissolution profiles of PHT formulated with HPC-SSL using various processing techniques

formulated by HMM using all of the polymers (Fig. 6). As identified during DSC and PLM analysis, the dissolution improvement of CBZ could be attributed to amorphous conversion as well as to dispersion of the API in hydrophilic polymers that occurred during the HMM process. The highest dissolution rate of CBZ was observed in Eudragit EPO HMMs and could be due to the very high solubility and dissolution rate of this basic polymer in 0.1 N HCl. Although the dissolution rate of CBZ : PVP-VA HMMs was highest amongst the non-ionic polymers tested, HMMs using low-viscosity HPC polymers also exhibited significant improvement in dissolution rate and extent as compared to the pure drug. The differences in extent of this improvement using various polymers can be attributed not only to their functional groups but also to differences in their hydrophilicity that may have influenced the wetting of the drugs in SDs. For instance, although PVP-VA and HPC are both non-ionic, PVP-VA with a vinyl backbone could be more readily hydrated or more surface active than cellulosic HPC (30), and perhaps leading to a higher dissolution rate and extent when incorporated into SDs than those of HPC. Besides, formation of SDs with hydrophobic drugs in their crystalline form may have changed the overall wetting of the SDs.

Unlike CBZ, the dissolution rate and extent of the weakly basic drug HCTZ itself was relatively high (Fig. 7). The crystalline solid dispersions of HCTZ that could be manufactured by HMM using the non-ionic polymers PVP-VA and HPC depicted dissolution profiles similar to that of the pure drug. On the other hand, HCTZ HMMs of HPMCAS-LF and Eudragit L-100-55 showed slight improvement in the dissolution rate as compared to the pure drug, which could be due to the counter-ionic interactions and hydration between weakly basic HCTZ and these anionic, polycarboxylate polymers.

As shown in Fig. 8, the dissolution rate and extent of PHT was slightly enhanced by both non-ionic (HPC) and anionic (HPMCAS-LF and Eudragit L-100-55) polymers, perhaps due to the formation of crystalline solid dispersions of the drug in these hydrophilic polymers during the HMM process. However, the dissolution rate of PHT was significantly reduced for PHT: PVP-VA HMMs, probably due to the formation of hydrophobic lumps observed during the dissolution process that neither dispersed nor eroded rapidly. The significant enhancement in dissolution rate and extent of acidic PHT using the basic polymer Eudragit EPO could be attributed to counter-ionic drug–polymer interactions as well as to the very high solubility and dissolution rate of the polymer in 0.1 N HCl.

Since the melting point of PHT is very high (>290°C), it was noted that the drug could not be mixed and dispersed thoroughly with the HPC polymers during HMM process even at the operating temperature as high as 180°C. Hence, solvent evaporation (SE) and ball mill (BM) products of PHT with HPC-SSL were manufactured in order to investigate the processibility of HPC-SSL using these alternative formulation methods. Although the drug could not be converted into its amorphous form using any of these processes as revealed by DSC and PLM analyses, the enhancement in dissolution rate of PHT was in the order of SE>BM>HMM, and lastly PM, as compared to the pure drug (Fig. 9). The better performance of SE and BM products could be due to more intimate mixing and physical dispersion of PHT in HPC-SSL that could have occurred during these processes as compared to HMM, as well as to the formation of much smaller drug particles by more vigorous mechanical milling during the BM process.

As depicted in Fig. 10, slower release of the otherwise highly soluble BCS class I drug CPM could be achieved at both gastric (pH 1.2) and intestinal (pH 6.8) conditions when using low-viscosity HPC polymers. The tablets produced using the PMs exhibited slower, more sustained release as compared to tablets analogously manufactured from the corresponding

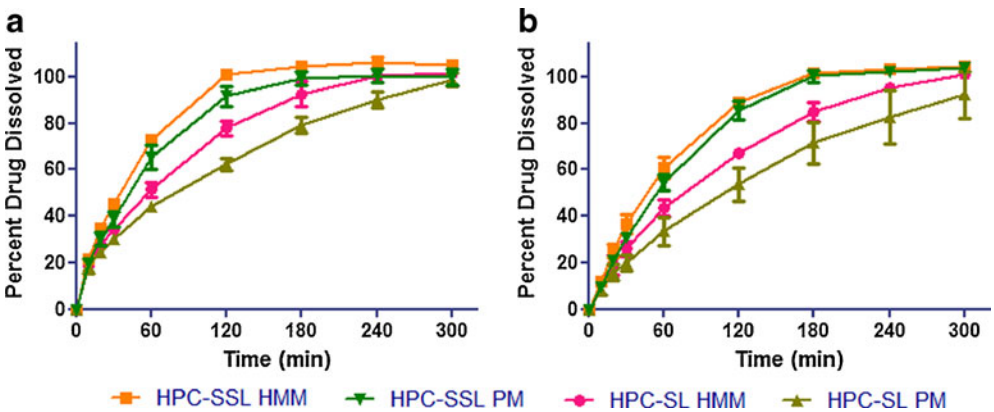

Fig. 10. Dissolution profiles of CPM tablets containing HMMs and PMs formulated with HPC-SL and HPC-SSL in **a** 0.1 N HCl and **b** phosphate buffer pH6.8

HMMs. This might be attributed to amorphous conversion of the drug during the HMM process that could have improved the aqueous solubility of CPM. The performance of the HPC-SL polymer in controlling the release of CPM was better than that of HPC-SSL, perhaps because the higher bulk viscosity of HPC-SL was manifested as slower release rate as compared to the less viscous HPC-SSL in both PM and HMM tablets. Although the release of CPM was slowed using HPC during *in vitro* dissolution studies, it may not necessarily predict similar results *in vivo* unless IVIVR has been established. The stronger hydrodynamic flow and mechanical peristalsis in the human gastrointestinal tract as compared to a model USP dissolution apparatus might still lead to more rapid tablet disintegration, particle wetting, and faster release of the drug *in vivo*.

CONCLUSION

Low-viscosity HPC-SL and -SSL polymers were found to be suitable excipients for producing chemically stable HMM products at the processing temperature and speed wherein several other polymers caused degradation of the API's. Like other polymers, HPC-SL and -SSL could be used to convert the relatively high melting crystalline drug CBZ into its amorphous form using HMM, which improved the dissolution characteristics of the drug. Although amorphous conversion of very high melting drugs such as PHT could not be achieved using HMM, the dissolution rate and extent of PHT could be significantly improved by manufacturing crystalline dispersions in HPC-SSL using other techniques, namely BM and SE. In addition, HMM technology could be successfully employed to sustain the release of the highly water-soluble drug CPM using HPC-SL and -SSL in both gastric and intestinal pH conditions. In conclusion, low-viscosity HPC-SL and -SSL polymers are versatile excipients that may be employed in a variety of formulation processes in order to produce chemically stable formulations of both poorly and highly water-soluble drugs with desirable dissolution and release characteristics.

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