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Research paper

Fusion production of solid dispersions containing a heat-sensitive active ingredient by hot melt extrusion and Kinetisol® dispersing

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ABSTRACT

Many techniques for the production of solid dispersions rely on elevated temperatures and prolonged material residence times, which can result in decomposition of temperature-sensitive components. In this study, hydrocortisone was used as a model temperature-sensitive active ingredient to study the effect of formulation and processing techniques as well as to characterize the benefits of KinetiSol® Dispersing for the production of solid dispersions. Preformulation studies were conducted using differential scanning calorimetry and hot stage microscopy to identify optimum carriers for the production of amorphous solid dispersions. After identification, solid dispersions were prepared by hot melt extrusion and KinetiSol® Dispersing, with material characterized by X-ray diffraction, dissolution and potency testing to evaluate physicochemical properties. Results from the preformulation studies showed that vinylacetate:vinylpyrrolidone (PVPVA) copolymer allowed for hydrocortisone dissolution within the carrier at temperatures as low as 160 °C, while hydroxypropyl methylcellulose required temperatures upward of 180 °C to facilitate solubilization. Low substituted hydroxypropyl cellulose, a high glass transition temperature control, showed that the material was unable to solubilize hydrocortisone. Manufacturing process control studies using hot melt extruded compositions of hydrocortisone and PVPVA showed that increased temperatures and residence times negatively impacted product potency due to decomposition. Using KinetiSol® Dispersing to reduce residence time and to facilitate lower temperature processing, it was possible to produce solid dispersions with improved product potency. This study clearly demonstrated the importance of carrier selection to facilitate lower temperature processing, as well as the effect of residence time on product potency. Furthermore, KinetiSol® Dispersing provided significant advantages over hot melt extrusion due to the reduced residence times and lower required processing temperatures. This allowed for the production of solid dispersions with enhanced product potency.

1. Introduction

Manufacturing techniques for the production of solid dispersions have gained increasing popularity as the number of poorly water-soluble compounds has increased. Two unit operations that have gained significant popularity for this application are spray drying [1–3] and hot melt extrusion [4–6]. During spray drying, the drug and carrier are dissolved in a common miscible solvent, sprayed into a drying chamber and the solvent evaporated from the system to produce solid dispersion. In hot melt extrusion, the drug and carrier are processed under significant agitation at elevated temperatures, yielding solid dispersions upon cooling. While solvent-based systems such as spray drying have been employed successfully in the production of amorphous solid dispersions, this technique involves the use of potentially toxic solvents, presenting substantial issues in terms of residual solvents. In some cases, it may be necessary to process at elevated temperatures and provide continued drying. Similarly, hot melt extrusion requires the use of substantially elevated temperatures that pose limitations for thermally sensitive active ingredients and carriers alike. While elevated processing temperatures are widely acknowledged as a significant limitation to current production technologies [7], only limited studies have been undertaken to characterize the decomposition of thermally sensitive materials in pharmaceutical systems.

During the extrusion process, degradation of materials results from thermal and mechanical factors which occur during

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processing. In many polymer processing studies, degradation has been reported to occur via thermal mechanisms [8,9], and it is well known that degradation rates of many pharmaceutical active ingredients increase at elevated temperatures [10]. In a recent study by Repka and co-workers, hot melt extrusion was investigated as a method of producing clotrimazole films for the treatment of oral candidiasis [11]. Although the authors concluded that the manufacturing process was a viable method for the production of such films, degradation of clotrimazole to (o-chlorophenyl) diphenyl methanol resulted in product potencies of approximately 93%. In another study by Repka and co-workers, films of hydrocortisone and chlorpheniramine maleate were prepared in hydroxypropyl cellulose to assess the effect of the active ingredient on the physicomechanical properties of the films [12]. Results showed that films prepared containing chlorpheniramine maleate provided acceptable product potencies, while formulations containing hydrocortisone exhibited increased decomposition at elevated temperatures. During processing, the researchers concluded that hydrocortisone degraded at elevated temperatures due to oxidation to a D-homosteroid. This behavior indicated that increases in thermal exposure due to increased temperatures accelerated decomposition. One strategy to reduce processing temperatures is through the incorporation of a plasticizer, which is frequently employed to facilitate manufacturing of thermally sensitive actives and carriers [13–15]. In a recent study by Verreck et al., supercritical carbon dioxide was used as a temporary plasticizer to facilitate production of p-amino salicylic acid at lower temperatures [16]. Compositions produced without the supercritical fluid required the use of elevated temperatures which resulted in greater decomposition compared to plasticized formulations, which provided up to 95% product potencies.

For many cases, thermal degradation of a material is primarily related to cumulative exposure, which is a function of temperature and duration. In order to minimize thermal degradation of pharmaceutical components under elevated temperatures, techniques incorporating suitable formulation design to limit degradation and appropriate process optimization to reduce thermal exposure may be utilized. Many systems manufactured by hot melt extrusion require temperatures above the glass transition temperature of the carrier and melting point of the active ingredient to facilitate processing. It is also possible to render an amorphous solid dispersion by processing below the melting point of the active ingredient by selecting carriers capable of solubilizing the drug substance within the molten carrier. This behavior, however, is not universal to all drug:carrier combinations, but rather depends on the interplay of the pair's physicochemical properties. Solubility parameters have been extensively used to predict the miscibility of such compositions [17] and in many cases miscibility can also imply solubility of the drug within the polymeric matrix. In order to exploit this synergistic behavior, it is critical to identify appropriate combinations at an early stage using preclinical characterization techniques. In several studies reported by Forster and co-workers, a variety of preclinical characterization techniques were utilized to assess drug:carrier compatibility [18,19]. Solubility parameters provide a preliminary indication of the interaction between the drug and carrier based on the chemical composition of the materials. It is generally accepted that interaction parameter differences of less than 7 $MPa^{1/2}$ will lead to favorable interactions between the components, while differences greater than 10 $MPa^{1/2}$ will lead to unfavorable behavior and phase separation. Although this provides an indication of the behavior of the system and can be used to identify potential combinations that may process favorable interactions, it does not directly quantify the behavior of such systems under conditions analogous to production. In order to assess the behavior under thermal processing conditions, hot stage microscopy and differential scanning calorimetry have been applied to assess processability of drug:carrier physical mixtures [18]. Mixtures of the drug and carrier can be visually assessed using hot stage microscopy to image drug dissolution within the carrier, as well as recrystallization of the drug from the polymer upon cooling. Similarly, differential scanning calorimetry can be used to assess drug:carrier compatibility. The heating process applied during DSC testing is analogous to the thermal exposure that the materials experience during processes such as hot melt extrusion. Regulation of the heating rate can control the recovery of materials during testing, such that slower heating rates allow for greater duration of drug dissolution in the carrier. This behavior has been shown to limit the ability to detect crystalline material in a solid dispersion and is a major reason for using a secondary "cold" method such as X-ray diffraction in the assessment of crystal content. However, application of DSC to physical mixtures can provide an indication of drug dissolution rate within the carrier and can be used to identify optimum compositions.

Processing of solid dispersions below the active ingredient melting point has also been well established as a method to produce amorphous compositions. Trey et al. [20], successfully prepared hot melt extruded films of itraconazole and hydroxypropylcellulose at 155 °C, below the melting point of itraconazole. Similar behavior has also been reported by Miller et al. for systems of itraconazole and Eudragit® L100-55 [21] as well as Chokshi et al. for combinations of indomethacin and PVPVA [22]. Utilizing a similar approach, Lakshman et al. [23] preprocessed high melting point temperature-sensitive active ingredients by spray drying to render the material amorphous prior to processing at significantly reduced temperatures to minimize degradation in order to render an amorphous solid solution by melt extrusion. While these low temperature-processing approaches have been utilized to facilitate production of various compositions, few publications report the direct use of carrier selection to complement the manufacture of heat-sensitive ingredients using fusion methods.

Fusion manufacturing methods have been well established in academic research for the production of solid dispersions; however, the primary manufacturing method for this class of techniques is hot melt extrusion [13–15]. Having been extensively utilized for the production of solid dispersions for bioavailability enhancement, controlled release and dosage form design such as films and shaped tablets, hot melt extrusion has emerged as one of the premier production methods. While numerous advantages of this process have been cited, the high temperatures required and possibility for extended residence times of up to 10 min [16] can limit the applicability for production with temperature-sensitive materials.

KinetiSol® Dispersing is a new fusion-based manufacturing that utilizes a combination of frictional and shear energies to rapidly produce solid dispersions [24,25]. This technique has been successfully employed for the production of hydrophilic solid dispersions and plasticizer-free solid dispersions containing temperature-sensitive polymers such as Eudragit® L100-55 [24,25]. In this study, it was hypothesized that potency of hydrocortisone solid dispersions produced by thermal manufacturing techniques could be improved through the correct identification of carrier materials and the application of novel manufacturing technologies such as KinetiSol® Dispersing. Under the study design, preclinical characterization of drug and polymeric carriers were conducted using differential scanning calorimetry, hot stage microscopy and thermal gravimetric analysis. Following identification of appropriate polymeric carrier materials, a design of experiments was conducted to study the effect of hot melt extrusion processing variables such as screw speed, residence time and temperature on the finished product attributes. Finally, compositions were also prepared using KinetiSol® Dispersing and evaluated for potency, dissolution and crystal character in comparison with hot melt extruded material.

2. Materials and methods

2.1. Materials

Micronized hydrocortisone, USP (HCT) was purchased from Spectrum Chemical Co. (Gardena, CA). Kollidon® VA64, a vinylpyrrolidone–vinylacetate copolymer (6:4) (PVPVA 64), low substituted hydroxypropyl cellulose (L-HPC) and hydroxypropyl methylcellulose (2910 grade) (HPMC E3) were donated by BASF Corporation (Florham Park, NJ), Shin Etsu and Dow Chemical Corporation (Midland, MI), respectively. HPLC grade acetonitrile and methanol were purchased from EMD chemicals (Darmstadt, Germany). All other chemicals utilized in this study were of ACS grade.

2.2. Methods

2.2.1. KinetiSol® Dispersing (KSD)

KinetiSol® Dispersing was performed using a custom built compounder designed for pharmaceutical processing applications by DisperSol Technologies, L.L.C. (Austin, TX) as described previously [24,25]. Prior to processing, drug and polymer compositions were accurately dispensed into an impact mill and premixed for 1 min prior to being charged into the compounder. During processing, temperature and rotational speeds were monitored with material discharged immediately upon achieving the target processing temperature. During production, PVPVA 64 and HPMC E3 compositions were prepared using maximum rotational speeds of 3200 rpm and 2200 rpm, respectively. Following discharge, the material was quench pressed, as necessary, between two chilled plates, ground using an impact mill (Capresso Inc., Closter, NJ) and passed through a 60-mesh (250 μm) screen prior to further testing. In-process temperature profiles were smoothed using a five-point mean value algorithm and plotted using Microsoft Excel 2003 (Microsoft Corporation, Redmond, WA).

2.2.2. Hot melt extrusion (HME)

Hot melt extrusion was conducted using a co-rotating conical (5/14 mm diameter) twin screw HAAKE Minilab II Microcompounder (Thermo Electron Corporation, Newington, NH). Compositions using PVPVA as a carrier were prepared using the 2-mm round opening die, while no die was used for compositions produced with HPMC E3. Prior to processing, materials were accurately weighed, premixed in an impact mill for 1 min (Capresso Inc., Closter, NJ) and manually charged into the extruder during processing to provide a continuous feed. As necessary, recirculation was used to achieve required residence time. Powder blends and appropriate manufacturing conditions for each batch are detailed in Table 1. Following extrusion, extrudates were milled using an impact mill (Capresso Inc., Closter, NJ) and screened using a 60-mesh sieve to yield a final powder for analysis.

2.2.3. Residence time studies

To assess the residence time of hydrocortisone and PVPVA formulations, a dye tracer was utilized to visually identify the residence time of material in the barrel. For these studies, a spike blend containing 10% hydrocortisone, PVPVA 64 and yellow tracer dye (Sensient, Milwaukee, WI) having a bright orange color was prepared by replacing approximately 2% of PVPVA 64 with dye and thoroughly mixed in a glass mortar and pestle. During testing, the extruder was preset to the required conditions. HCT:PVPVA 64 powder in a 1:9 ratio was mixed and charged into the extruder hopper. At a predetermined time, approximately 500 mg of dye-containing mixture was charged into the extruder hopper followed by continued charging of the dye-free powder blend. Upon charging the dyed material, transit was timed by visual identification of a color change.

Table 1
HME manufacturing conditions of batches produced for screening studies and factorial DOE.

Batch ID	Polymer	Temperature (°C)	Screw speed (RPM)	Recirculation time (min)	Torque (Nm)	Potency (%)
001	HPMC	160	50	0	290 ± 35	NA
002	HPMC	180	50	0	114 ± 30	75.0 ± 0.4
003	HPMC	200	50	0	49 ± 5	50.6 ± 0.3
004	HPMC	230	50	0	20 ± 5	17.3 ± 0.8
005	PVPVA	160	50	0	24 ± 4	97.4 ± 0.3
006	PVPVA	160	50	5	27 ± 4	96.7 ± 0.4
007	PVPVA	160	150	0	83 ± 7	97.7 ± 0.8
008	PVPVA	160	150	5	86 ± 7	95.8 ± 1.0
009	PVPVA	180	50	0	15 ± 3	95.7 ± 1.1
010	PVPVA	180	50	5	15 ± 3	95.4 ± 0.8
011	PVPVA	180	150	0	58 ± 11	96.6 ± 1.3
012	PVPVA	180	150	5	53 ± 5	93.6 ± 0.7
014	PVPVA	200	50	0	11 ± 3	94.6 ± 0.4
015	PVPVA	200	50	5	11 ± 4	88.6 ± 1.0
016	PVPVA	200	150	0	35 ± 4	94.8 ± 2.6
017	PVPVA	200	150	5	37 ± 5	89.4 ± 2.9

2.2.4. Thermal gravimetric analysis

Thermal gravimetric analysis was conducted using a Perkin–Elmer 7-Series Thermogravimetrical Analyzer (Norwalk, CT) operated at a ramp rate of 10 °C/min from a temperature of 50 °C to 350 °C. Samples were prepared by degassing under desiccated vacuum for 72 h at room temperature prior to analysis and accurately measuring a sample of approximately 10 mg. Data were analyzed using Perkin–Elmer control software and plotted using Microsoft Excel.

2.2.5. Differential scanning calorimetry screening studies

Differential scanning calorimetry (DSC) testing was conducted using a TA Instruments Model 2920 DSC (New Castle, DE) and analyzed using TA Universal Analysis 2000 Software. Prior to testing, physical mixtures of drug and carrier were prepared in a glass mortar and pestle by accurately dispensing the components and manually mixing for 2 min. Samples were accurately weighed to 15 ± 2 mg in aluminum-crimped pans (Kit 0219-0041, Perkin–Elmer Instruments, Norwalk, CT). Testing was performed from 50 to 250 °C at a ramp rate of 10 °C/min under nitrogen purge at a flow rate of 40 mL/min.

2.2.6. Hot stage microscopy screening studies

Characterization of HCT solubility in the molten carrier was assessed using hot stage microscopy. Polymer samples were prepared by dissolving PVPVA in acetone and HPMC E3 in purified water. The solutions were pipetted onto a glass slide and allowed to dry at 25 °C for a minimum of 24 h prior to testing. Prior to testing, HCT was spread onto the polymer-coated surface of the slides. As a control, HCT was also tested by spreading across an uncoated slide and observed under heating. During testing, an Olympus BX60 microscope (Olympus Corp., Center Valley, PA) with Insight QE camera (Diagnostic Instruments, Inc., Sterling Heights, MI) was used to visually observe samples, while a FP82HT hot stage controlled by a FP 90 central processor (Mettler Toledo, Columbus, OH) maintained temperatures at 160 °C for 15 min followed by an additional 15 min at 180 °C. Images were captured under visible and polarized light using Spot Advance Software (Diagnostic Instruments, Inc.) after reaching 160 ± 2 °C, after 15 min at 160 ± 2 °C and after an additional 15 min while being maintained at 180 ± 2 °C.

2.2.7. X-ray diffraction (XRD)

XRD testing was performed using a Philips Model 1710 X-ray diffractometer (Philips Electronic Instruments Inc., Mahwah, NJ) to assess crystallinity in conjunction with thermal techniques. Processed powders were tested after screening through a 60-mesh screen, as described previously. Physical mixtures were prepared by premixing HCT and polymer in the appropriate ratio prior to analysis. Samples of powder were placed into channeled stages, and the diffraction profile was measured from 5° to 50° using a 2θ step size of 0.05° and dwell time of 3 s.

2.2.8. Assay testing

Finely ground powder samples were accurately weighed to 100.0 ± 3.0 mg and transferred directly into a 100-ml volumetric flask. Measured powder samples were dissolved using a 1:1 methanol:water solution and diluted to 100 mL total volume. Samples were then filtered using 13-mm 0.2-mm PTFE filters (Whatman, Piscataway, NJ) and transferred into HPLC vials for analysis (VWR International, West Chester, PA) for analysis.

2.2.9. In vitro dissolution

Dissolution testing (USP XXIX, Apparatus II) was performed using a VK 7010 dissolution apparatus (Varian, Inc., Palo Alto, CA) operated at 50 rpm paddle speed and VK 8000 autosampler (Varian, Inc., Palo Alto, CA). An equivalent amount of 25.0 ± 0.3 mg of HCT (theoretical drug loading) was accurately weighed and added to the dissolution vessel containing 900 mL of 0.1N HCl media preheated to 37 °C. During testing, 5 mL samples were removed from the dissolution vessels without replacement after 5, 10, 15, 30, 45 and 60 min. Samples were immediately filtered using 0.2-μm PTFE membrane and 13-mm filters (Whatman, Piscataway, NJ) and transferred into 1-mL vials (VWR International, West Chester, PA) for analysis.

2.2.10. HPLC analysis

Assay and dissolution samples were analyzed using a Waters (Waters Corporation, Milford, MA) high performance liquid chromatography (HPLC) system consisting of dual Waters 515 Syringe Pumps, a Waters 717 Autosampler and a Waters 996 Photo Diode Array extracting at a wavelength of 254 nm and 242 nm, respectively. The system was operated under isocratic flow at 1 mL/min using a mobile phase consisting of 2:1:1 water:acetonitrile:methanol. For assay testing, a Phenomenex Luna 5 μm C18(2) 100 Å, 250 mm × 4.6 mm (Phenomenex®, Torrance, CA) HPLC column was used to facilitate separation of major impurities, while a Phenomenex Luna 5 μm C18(2) 100 Å, 150 × 4.6 mm (Phenomenex®, Torrance, CA) was used for dissolution testing. Sample injection volumes of 50 μL were used during testing. Data were collected and analyzed using Empower® Version 5.0 software, and all analytical tests maintained system suitability linearity and reproducibility of $r^2 \geqslant 0.999$ and % RSD $\leqslant 2.0\%$, respectively.

2.2.11. Statistical analysis

Factorial design of experiments and statistical analysis was conducted using Minitab Release 14 (Minitab, Inc., State College, PA). For analysis, experimental designs were analyzed using Minitab analyzer modules. Additional analysis was conducted using ANOVA with Tukey post hoc testing. A p value of <0.05 was considered statistically significant.

2.2.12. Solubility parameter calculations

Hansen solubility parameters for compositions not referenced from literature were calculated based on molecular structure and melting point using Molecular Modeling Pro, v 6.2.8 (ChemSW, Fairfield, CA).

3. Results and discussion

3.1. Preclinical characterization

Material stability at elevated temperatures is an essential prerequisite for successful solid dispersion production using fusion processing and several techniques can be employed to assess material stability under elevated conditions. One such technique is TGA, which can be utilized to determine the weight loss of a material measured under isothermal or dynamic temperature conditions and has been frequently applied to assess the thermal stability of materials prior to hot melt extrusion. HCT and the polymeric carriers HPMC E3 and PVPVA 64 were tested using TGA to assess their thermal stability, as shown in Fig. 1. As shown in the weight loss profiles, all materials exhibited minimal weight loss through temperatures of approximately 200 °C, although the calculated degradation onset temperature based on weight loss for HCT was approximately 180 °C. It is important to note that this method of decompositional measurement is only effective for materials that exhibit a change in weight during degradation. Samples of HCT were also maintained under isothermal conditions for 20 min at 160 °C, 180 °C and 200 °C in order to assess potency changes. Potency measurements showed limited decomposition at temperatures below 200 °C, supporting the TGA results (data not shown). At temperatures above 200 °C, rapid decomposition of all materials was observed which indicated that maximum processing temperatures should not exceed 200 °C for extended durations and would ideally be maintained below 180 °C.

Selection of appropriate drug:polymer combinations was performed on representative physical mixture preparations using differential scanning calorimetry and hot stage microscopy as shown in Figs. 2 and 3, respectively. Physical mixtures tested using DSC were compared to unprocessed polymer samples and examined for the presence of melting and drug dissolution events associated with HCT. For combinations of HCT and L-HPC, an endothermic event was observed at 220 °C, having an associated transition energy of 11.27 J/g. Noting that the formulation contained 10% HCT, which had a transition energy of 136 J/g, this value represents approximately 82% recovery of crystalline HCT from the test. Additionally, minimal depression of the HCT melting point is observed, indicating that L-HPC would not be a suitable carrier for processing HCT at temperatures significantly below its melting point. For HPMC, a similarly high recovery of crystalline HCT is observed at approximately 103%; however, a significant reduction in melting temperature is observed, having an onset of 171 °C. This suggests that HPMC would be more effective than L-HPC for processing HCT below the melting temperature and could potentially be achieved at temperatures as low as 170 °C. Physical mixtures of HCT and PVPVA 64 also tested by DSC did not exhibit a melting endotherm for HCT. In comparison with the unprocessed polymer sample, a downward drift in baseline above 130 °C was observed, which may be due to the dissolution of HCT in the molten PVPVA 64. The absence of a defined melting endotherm and the possible dissolution of HCT evidenced by the change in baseline suggest that the PVPVA 64 would function as an optimum carrier for solid dispersion processing, allowing for production at temperatures significantly below the melting point of the active ingredient.

In order to verify the data generated by DSC, hot stage microscopy studies were conducted to visually determine the onset, rate and extent of drug dissolution within the carrier. Images taken under optical and polarizing light are shown in Fig. 3. Samples of HCT layered directly onto the glass slide showed minimal change following heating through 180 °C, which was characteristic of the DSC that showed melting did not occur until approximately 220 °C. Since similar results were obtained in the DSC study for

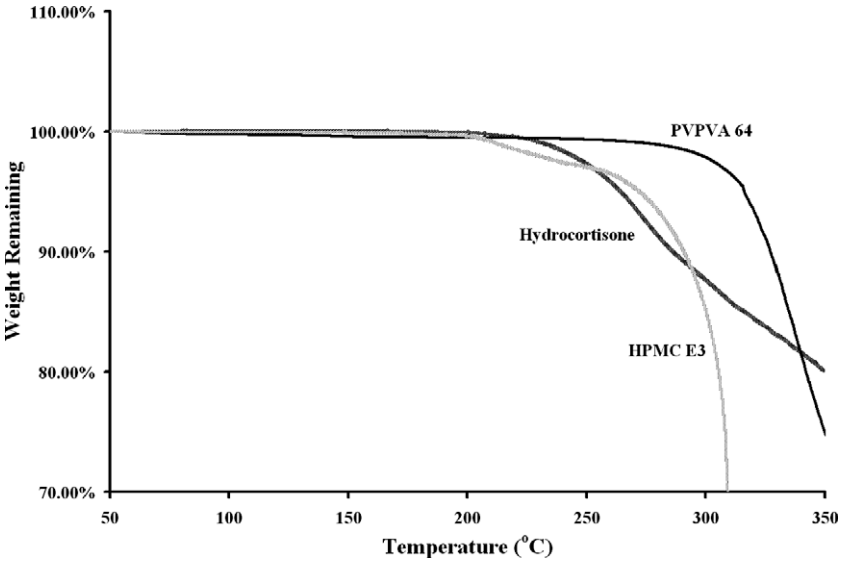

Fig. 1. TGA Profile for HCT, PVPVA 64 and HPMC E3.

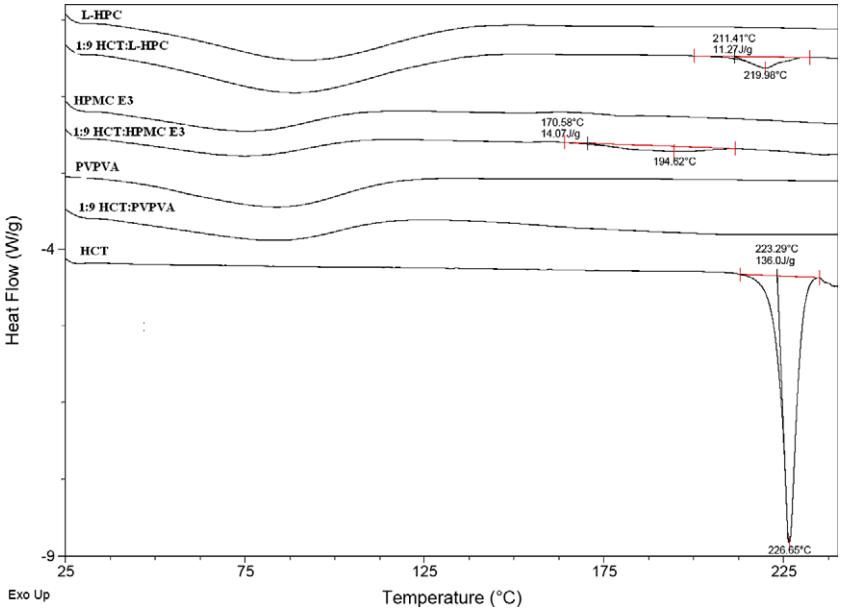

Fig. 2. Excipient screening by differential scanning calorimetry. Physical mixtures were prepared in a 1:9 ratio using a mortar and pestle. Testing conducted at a ramp rate of 10 °C/min. (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

L-HPC that showed no solubilization or melting point depression benefit, this combination was not tested. In strong agreement with the DSC data, HCT layered onto HPMC E3 showed minimal API dissolution until reaching temperatures of 180 °C and thereafter showed extensive solubilization of the drug. For combinations of HCT and PVPVA 64, optical imaging showed that the drug was extensively solubilized at temperatures as low as 160 °C, again being well correlated with the results obtained by DSC testing.

Examination of the solubility parameters for each of the components was also conducted to rationalize the behavior observed during screening. Based on the molecular structure, the Hansen solubility parameter for HCT was calculated to be 22.6 $MPa^{1/2}$. For the carriers, solubility parameters of 22.9 $MPa^{1/2}$ and 30.0 $MPa^{1/2}$ for PVPVA [17] and HPMC 2910 [26] have been reported previously. Miscibility between components is commonly predicted when the difference between the solubility parameters of the materials is less than 7 $MPa^{1/2}$ and immiscibility to occur if the difference is greater than 10 $MPa^{1/2}$. Examination of the solubility parameters for the HCT:PVPVA 64 composition showed minimal difference indicating similar interaction energies during mixing, while solubility parameters for the HCT:HPMC composition provided differences greater than 7 $MPa^{1/2}$, which may indicate potential hindered dissolution and immiscibility. Results from the screening studies indicated that PVPVA provided more efficient solubilization of HCT upon exposure to elevated temperatures, suggesting that solubility parameters may also provide good indicators for the ability of a drug to be solubilized within a material. Similar behavior was also observed for itraconazole and Eudragit® L100-55, which have solubility parameters of 26.1 $MPa^{1/2}$ and 27.0 $MPa^{1/2}$, respectively. It is interesting to note that in a previous study by DiNunzio and co-workers [25], hot stage microscopy failed to predict drug dissolution within the

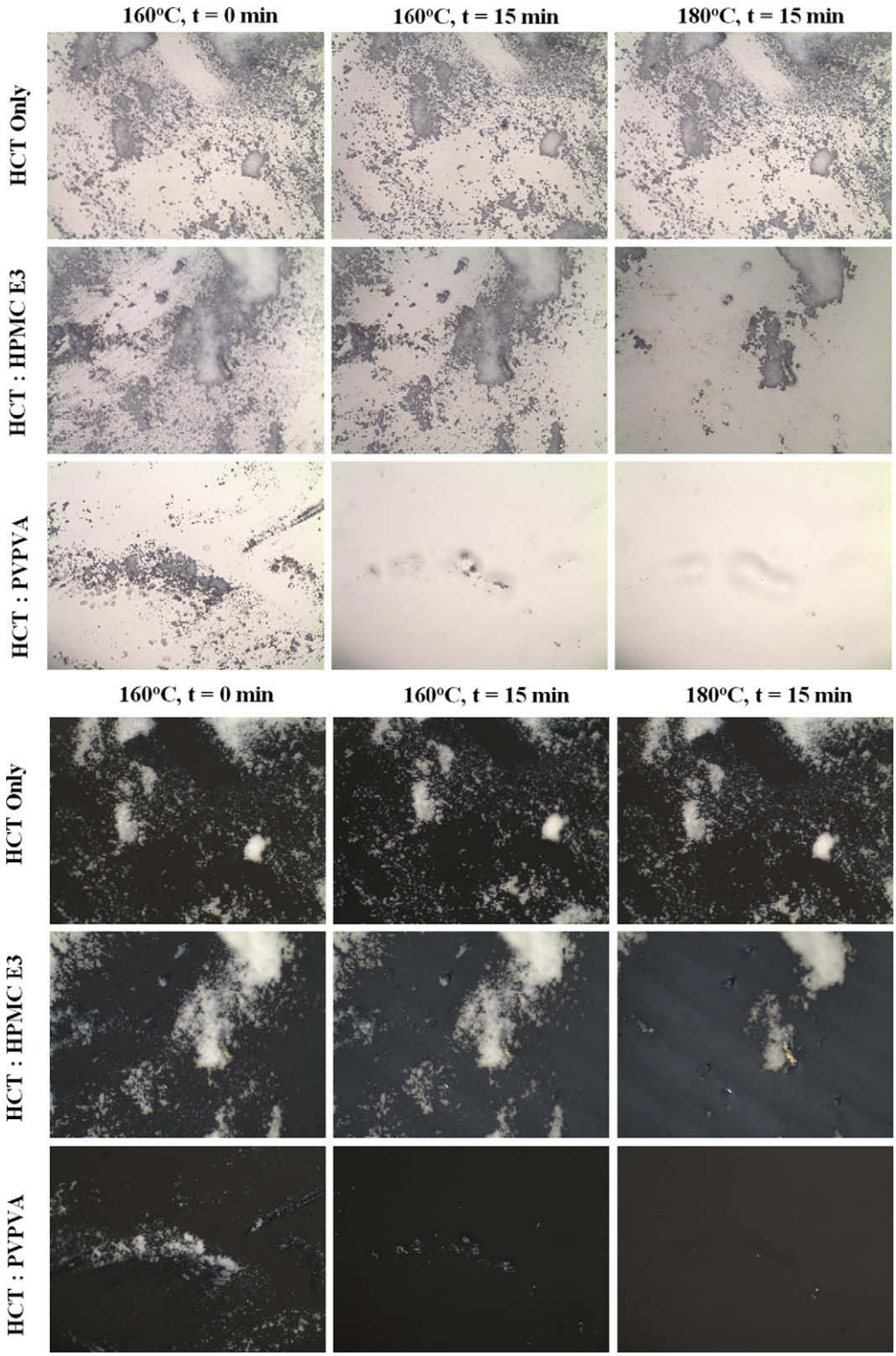

Fig. 3. Hot stage microscopy analysis of HCT dissolution in polymer samples by optical (top) and polarized (bottom) light. (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

polymer; however, subsequent production by hot melt extrusion and KinetiSol® Dispersing yielded amorphous product. This indicated that consideration of material properties and preformulation screening can provide insight into the melt behavior, however, may also be prone to the indication of false negatives due to the lack of shear provided by the characterization techniques presented here. It should also be noted that this behavior will depend on properties such as polymer molecular weight and drug diffusivity, and results gained during this stage of development should be leveraged with formulation experience under production settings.

3.2. HME process variable DOE

Previous studies of HCT solid dispersion production have shown that under thermal processing, degradation can occur [12]. In order to verify the behavior of the selected carrier materials, PVPVA 64 and HPMC E3, in terms of thermal processability and overall HCT decomposition profile, batches were prepared using the Haake minilab at different temperatures with a constant screw speed of 50 rpm and no additional recirculation. Samples were collected for assay analysis following extrusion and grinding, with measured potency values and in-process parameters presented in Fig. 4 and Table 1, respectively. During processing, HPMC E3 compositions were observed to have a lower overall material throughput and significantly higher torque loads which was attributed to the higher melt viscosity of the formulation. Attempts to manufacture this composition below 180 °C were unsuccessful and resulted in clogging. Conversely, formulations prepared by PVPVA exhibited better flow characteristics, however, could not be processed at temperatures above 200 °C due to insufficient viscosity of the material. Furthermore, differences in the potency profiles of the two formulations were also observed. Fig. 4 shows that the PVPVA 64 formulation provided minimal decomposition over the temperature range studied, while decomposition of the HPMC formulation was significantly influenced by the processing temperature. This disparity in potency at equivalent temperatures suggests the possibility of a specific drug:carrier interaction. In the previous work of Repka and co-workers, they identified the decomposition of HCT in HPC, which was attributed to an oxidation pathway. Examination of the molecular structure for HPMC shows similarity to HPC, specifically an abundance of hydroxyl groups which could potentially contribute to oxidation as free radicals. In a recent study by Basumallick et al. [27], it was shown that radical concentration of HPMC 2910 increased at temperatures above 120 °C, suggesting that the processing conditions of melt extrusion could facilitate propagation of oxidation during production. Examination of the potency chromatograms shows that the degradation products produced during extrusion of the PVPVA 64 composition also differ from those of the HPMC E3 composition. For the HPMC E3 formulation, one major impurity peak was observed similar to that reported by Repka and co-workers, which confirmed an oxidative decomposition. For compositions of HCT and PVPVA 64, three impurities were observed to form that were similar to those of thermally stressed HCT during TGA analysis and indicated that a second thermal mechanism was responsible for the decomposition. Differences in melt behavior were also observed and attributed to the thermoplastic characteristics of the carrier material used. PVPVA 64 exhibits a significant reduction in viscoelastic properties upon heating, while HPMC E3 is a non-thermoplastic polymer [28] and, therefore, required the presence of molten drug to lubricate flow. Since partially dissolved drug was required to achieve the requisite flow characteristics, higher temperatures were needed for processing. Flow resistance of the HPMC formulation also contributed to an observed reduced material output rate for this composition, increasing the residence time and further effecting decomposition. Based on the combined factors of specific drug:polymer interactions facilitating oxidation, requirements for elevated processing temperatures and the reduced product throughput, the HPMC E3 composition was not selected for the process study DOE. Instead, the PVPVA 64 composition, which provided higher potency and enhanced processing characteristics, was selected in order to determine the effect of processing variables including screw speed, temperature and residence time on finished product attributes.

During fusion production of solid dispersions, the overall thermal energy exposure as a function of temperature and residence time within the production equipment can play a significant role on the impurity profile of the finished product. HME is a continuous process and currently the preferred unit operation for the thermal production of amorphous solid dispersions in the pharmaceutical industry; however, the residence time of the material in the extruder barrel can be upwards of 10 min. During the process design phase, it is possible to reduce residence times within the equipment through proper screw design, screw speeds and material feed rates, as well as selection of appropriate equipment. For example, co-rotating twin screw extruders have been reported to provide shorter material residence times as a result of the self-wiping nature of the process [13]. Additional examples of process modulation include the replacement of mixing elements with conveying elements or increasing the screw speed to improve material transit. In order to better understand the effect of manufacturing process variables on the residence time of the HCT:PVPVA 64 formulation, a tracer dye was added to the formulation to allow for visual determination of material transit. Surface plots of the residence time and torque are presented in Fig. 5, and both character-

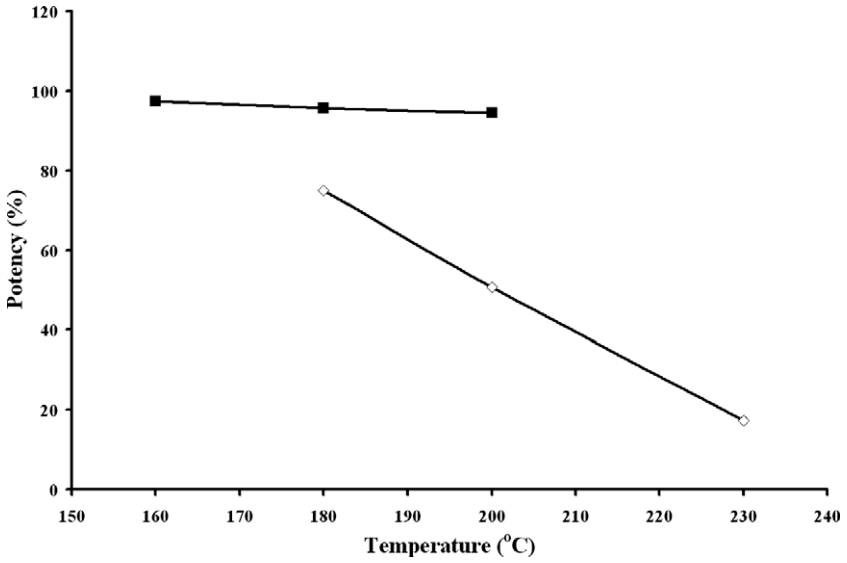

Fig. 4. Effect of temperature on product assay for HME processed solid dispersions containing HCT. Key: HPMC E3 (◇), PVPVA 64 (■).

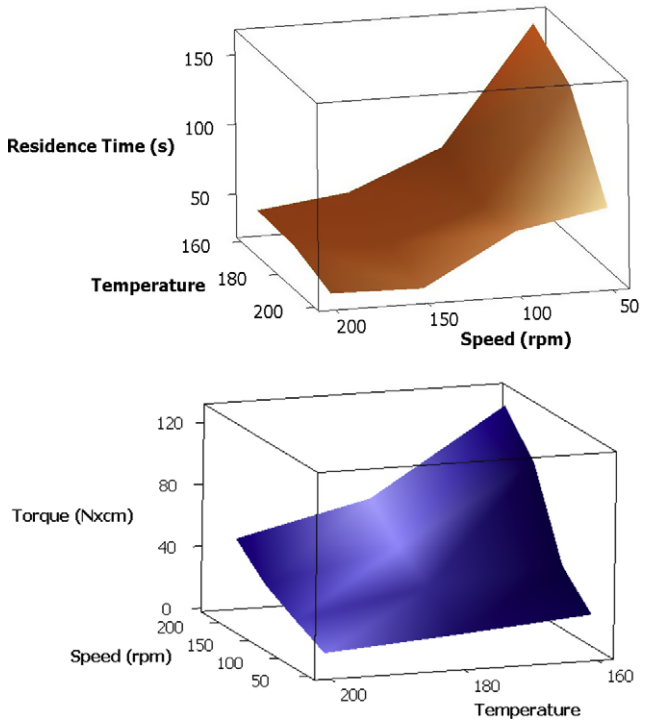

Fig. 5. Surface plot of the effect of process conditions on critical extrusion variables of residence time (above) and torque (below). (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

istics were shown to be strongly affected by screw speed and processing temperature. Torque provides an indication of the compositional viscosity during the extrusion process and is both a function of temperature and flow velocity for non-Newtonian polymer melts, including many pharmaceutical melts. The following equation shows the relationship between melt viscosity, which is proportional to torque, and temperature; where η is viscosity, K' is a constant, Ea is the activation energy of melt flow, R is the universal gas constant and T is temperature.

$$\eta = K' e^{Ea/RT}. \quad (1)$$

As temperature increases, the exponential relationship with viscosity provides improved material flow through a reduced viscosity. Similarly, increases in screw speed results in greater shear which drives a reduction in melt viscosity. Since viscosity is proportional to torque, the reduction of this metric can be correlated with the viscoelastic behavior of the material. Flow characteristics of the material within the extruder will be directly related to the viscosity of the melt and the conveying time which is a function of screw design and rotational speed. The behavior of residence time exhibited similar characteristics to that of torque, showing reductions of residence time due to increases in temperature and speed. For residence, time the major control variable was the screw speed. Material residence time was directly related to the screw speed as a result of extruder design, which regulates flow through screw flight, pitch angle and rotational speed [29]. In a fixed system, such as the Haake minilab, a threefold increase in rotational speed resulted in a corresponding increase in linear flow velocity. At lower screw speeds a more pronounced effect of temperature on screw speed was observed due to the higher viscosity of material. For higher temperature and lower viscosity formulations, residence time became limited only by the feed rate and slip which resulted from low material viscosity. These results indicated that it was possible to control residence time by maximizing screw speed and temperature, although elevation of temperature would also accelerate thermal decomposition.

A factorial design of experiments, presented in Table 1, was also conducted to examine the effect of processing variables on the potency of melt extruded compositions, specifically evaluating screw speed, temperature and residence time through the use of the recirculation collar. Fig. 6 shows the surface plots of potency as a function of critical variables in the study. Statistical analysis of the data, with p values presented in Table 2, revealed that residence time and temperature provided a statistically significant effect on product potency. Additionally, an interaction between residence time and temperature was resulted, which indicated that the cumulative thermal energy exposure was responsible for the decomposition of HCT in the system. Examination of batches with 5-min residence time revealed that screw speed, as well as the interaction of screw speed with temperature, did not have a statistically significant impact on product potency ($p > 0.05$). Shear during hot melt extrusion can also negatively impact product potency, and these results indicated that the HCT:PVPVA 64 system was not shear sensitive within the ranges studied in the Haake minilab.

During the development of a drug product, formulation and process development function synergystically to produce a system with optimum characteristics. For hot melt extrusion of a heat-sensitive active ingredient, control of the process variables can significantly impact the characteristics of the materials. By modulating the extruder processing conditions such as temperature, screw speed and geometry, it is possible to limit product residence time, which is essential since degradation is directly related to thermal exposure. While potency values for compositions without additional recirculation showed acceptable assay values above 95.0%, the addition of 5-min residence time resulted in further degradation. During scale-up, residence time within the extruder will generally increase relative to barrel length and may result in potency issues at the production scale that were not observed during laboratory-scale manufacture. Further control of process variables may mitigate residence time and improve potency; however, it is important to have a detailed understanding of the product behavior at both scales in order to develop an optimized manufacturing procedure.

3.3. Comparison of HME and KSD production

Study results identified during the DOE revealed that the combined effect of residence time and temperature contributed to the observed product potency of the HCT:PVPVA 64 solid dispersion. While small-scale extrusion without recirculation provided acceptable potency, achieving similar residence times on large-scale equipment may not be feasible due to differences in equipment

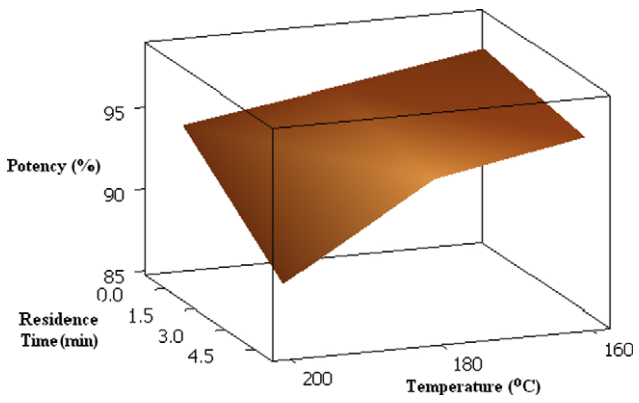

Fig. 6. Surface plot of 1:9 HCT:PVPVA 64 product potency as a function of processing conditions. (For interpretation of color mentioned in this figure the reader is referred to the web version of the article.)

Table 2
p Values for processing factors affect on potency from the factorial DOE.

Factor	*p*
Temperature (°C)	0.000
Screw speed (rpm)	0.777
Residence time (min)	0.000
Temperature (°C) × screw speed (rpm)	0.504
Temperature (°C) × residence time (min)	0.000
Screw speed (rpm) × residence time (min)	0.216
Temperature (°C) × screw speed (rpm) × residence time (min)	0.286

Table 3
Comparison of HCT solid dispersions prepared by KSD and HME processing.

Process	Polymer	Temperature (°C)	Additional residence time (min)	Assay (%)
KSD	HPMC E3	160	–	91.9 ± 0.8
KSD	HPMC E3	180	–	83.0 ± 0.3
HME	HPMC E3	180	–	75.0 ± 0.4
KSD	PVPVA 64	160	–	98.3 ± 0.2
HME	PVPVA 64	160	–	97.4 ± 0.3
HME	PVPVA 64	180	–	95.7 ± 1.1
HME	PVPVA 64	200	–	94.6 ± 0.4
HME	PVPVA 64	200	5	88.6 ± 1.0

geometry. KSD is a fusion process for the production of solid dispersions during which cycle times are generally less than 30 s and achieve the elevated temperatures only briefly. Additionally, as a result of the high shear involved, it may also be possible to process materials at reduced temperatures relative to hot melt extrusion. While geometric changes during scale-up associated with hot melt extrusion drive differences in residence time between scales, KSD is a semi-continuous process that provides nearly identical cycle times between the laboratory and production scale. In order to assess the effectiveness of KSD for the production of heat-sensitive solid dispersions, compositions of HCT in either PVPVA 64 or HPMC E3 were prepared and evaluated for potency, crystallinity and dissolution behavior using both manufacturing technologies.

Characteristic of the previously reported solid dispersions prepared by KSD, rapid cycle times were observed, which minimized thermal exposure [24,25]. Processing profiles for the batches produced are presented in Fig. 7. For both formulations, solid dispersions were rapidly prepared in less than 30 s, with exposure to temperatures above 130 °C experienced for less than 5 s. Similar to hot melt extrusion, decomposition in KSD would be regulated by mechanical and chemical decomposition accelerated by temperature. During the extrusion studies, decomposition of the formulations was shown to be independent of shear rate, which suggested that mechanical decomposition would not be significant. Utilizing the reduced thermal exposure provided by KSD, it was hypothesized that degradation could be minimized. Examination of product potency values presented in Table 3 showed that KSD provided improvements for both formulations, with a significant benefit observed for HPMC E3 solid dispersions. During extrusion studies, residence times of PVPVA 64 formulations were shown to be a strong function of the processing conditions, and many processing conditions were substantially longer than the 10-s processing cycle of HCT:PVPVA 64 formulations manufactured by KSD. For formulations prepared using HPMC E3, residence time studies were not conducted; however, material flow was observed to be more limited compared to the PVPVA 64 solid dispersions indicating longer residence times. Additionally, elevated temperatures were required to achieve flow resulting in greater thermal exposure of the product during processing. Using KSD, HPMC E3 formulations were processed in less than 30 s and were able to be processed at temperatures as low as 160 °C due to the combination of shear and frictional energy applied. The combination of lower temperatures and reduced residence times minimized thermal exposure and provided greater product potency.

The ability of the manufacturing process to render materials amorphous is essential for the development of solid dispersions for oral bioavailability enhancement. As demonstrated in the preformulation study, both carriers exhibited partial solubilization of the drug below the melting point of the API which limited the ability to assess amorphous character by DSC. For assessment of crystal content within the dispersion, XRD was implemented, and the results are presented in Fig. 8. HCT exhibits several strong characteristic crystalline peaks, of which those at 14.5 and 17.5 2θ are easily identifiable in representative physical mixtures. This allowed for an assessment of crystallinity within the solid dispersions produced. For all compositions, the diffraction patterns showed an amorphous halo and no crystalline peaks were de-

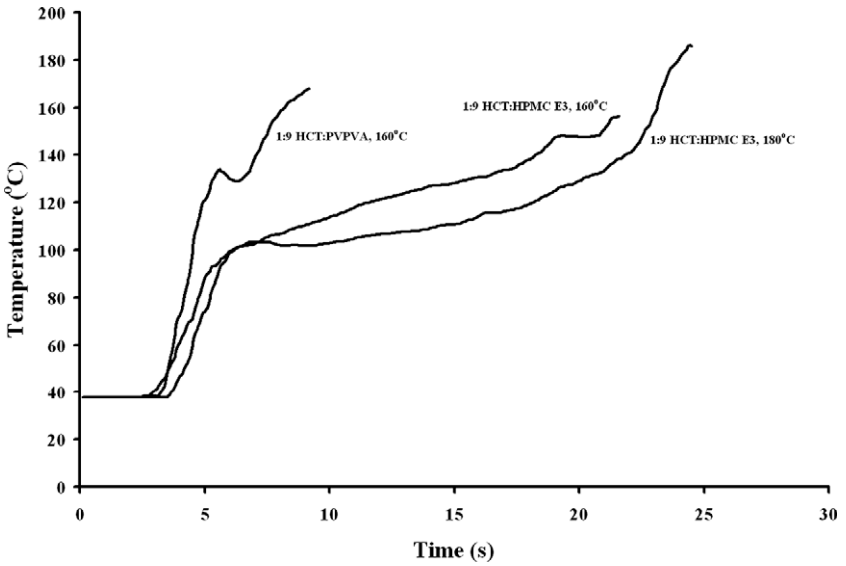

Fig. 7. KinetiSol® Dispersing manufacturing temperature profiles for HCT solid dispersions.

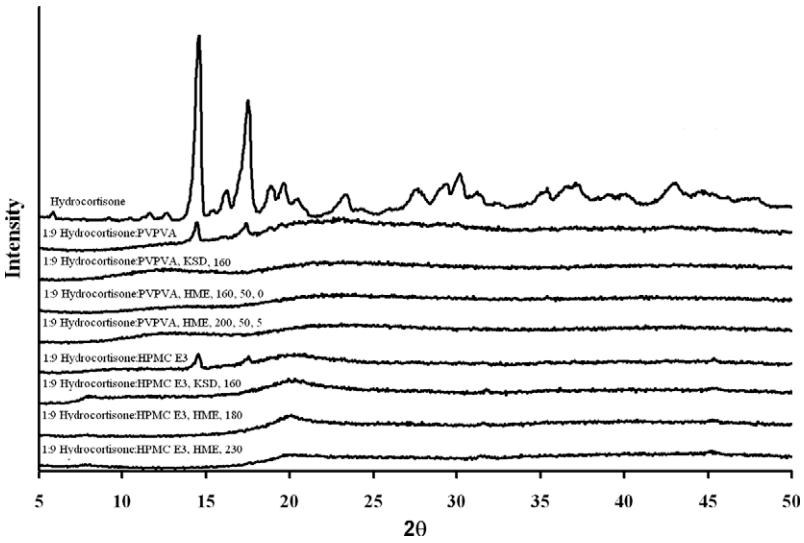

Fig. 8. XRD profiles of HCT, HCT:polymer physical mixtures and HCT:polymer processed solid dispersions.

tected, which indicated that HCT was present as an amorphous material within the carrier. Furthermore, based on the solubility parameter calculations, the PVPVA formulation would be predicted to yield a homogeneous solid dispersion while the HPMC composition could exhibit immiscible behavior. While the observed behavior indicated the formation of a solid dispersion, characterization of the homogeneity of the composition produced could not be assessed by conventional DSC methods due to solubilizing nature of the carriers. Recent studies, however, have illustrated the use of a potential new technology, Hyper-DSC, for the characterization of such systems which allows for a rapid heating rate to analyze compositional behavior [30]. Application of this technology may have provided additional insight into the nature of the type of solid dispersions formed in each formulation. Further examination of the XRD profile for the thermally processed HPMC compositions revealed a secondary low angle transition. While this may be due to noise associated with the test, it may also suggest phase separation and immiscibility between the HPMC and HCT, supporting the theoretical behavior suggested by the solubility parameters of compositional immiscibility.

In order to assess the dissolution rate enhancement provided by these compositions, dissolution testing of the powders was conducted under sink conditions. Results for dissolution testing of the HCT:PVPVA 64 and HCT:HPMC E3 compositions are presented in Fig. 9a and b, respectively. Examination of the profiles for each composition shows that the absolute release was strongly affected by the potency of the formulation, with all formulations providing faster release rates than unprocessed HCT. For compositions produced with PVPVA 64, higher potencies were achieved and, therefore, the magnitude of dissolution was also substantially greater than that observed with the HPMC E3 compositions. Also, compositions prepared with PVPVA carrier showed more rapid release than their HPMC counterparts, releasing nearly all material in less than 10 min while cellulosic solid dispersions provided slightly lower release rates. If the solid dispersion releases HCT via a polymer-mediated process, the dissolution rate of the carrier will become the rate limiting step [31]. The disparity in release rates, although minor, was most likely due to the gelling nature of HPMC which impedes carrier dissolution due to the formation of a diffusion barrier at the bulk interface.

While both manufacturing methods were capable of producing amorphous solid dispersions, carrier selection and mode of manufacture significantly influenced product potency. Formulations prepared by KSD exhibited higher potency values, and the magnitude of improvement between the two processes would be expected to increase in scaled-up systems having increased extruder residence times. Dissolution rate was also impacted by the selection of the carrier, although the magnitude of the difference between carriers was not significant when evaluated in comparison with the unprocessed crystalline API. These results indicate that both KSD and HME are acceptable techniques for the production of amorphous solid dispersions; however, formulation and process optimization must be performed to ensure maximization of critical product attributes. Utilization of KSD processing for the production of solid dispersions can provide critical advantages in terms of reduced processing temperatures and shortened residence times that can potentially lead to higher potency solid dispersions.

4. Conclusions

The limitation of fusion processing of heat-sensitive active ingredients due to elevated temperatures is one of the major perceived drawbacks in applying these techniques to solid dispersion production. One effective method for producing solid dispersions of such compounds is to select carriers that limit decompositional behavior at elevated temperatures and also facilitate processing at reduced temperatures to limit thermal exposure. As shown in the process parameters study, residence within the equipment was strongly influenced by operational conditions and was also shown to directly impact product potency. While the design of melt extruders can be configured to reduce residence time, issues on scale-up with increased residence times may also lead to greater degradation. KSD provided improved product potencies for both formulations in comparison with HME which was attributed to the reduced residence time of the compositions. This novel manufacturing technology also allowed for production of amorphous solid dispersions at lower temperatures, providing greater flexibility for processing heat-sensitive components. Since production cycle times are not significantly increased on scale-up, this technology may provide a viable platform for producing solid dispersions of thermally labile active ingredients when used in combination with formulations developed to facilitate processing at reduced temperatures and minimize degradation. By applying proper formulation techniques and novel manufacturing processes such as KSD, it is possible to produce amorphous solid dispersions of thermally labile active ingredients using fusion methods.

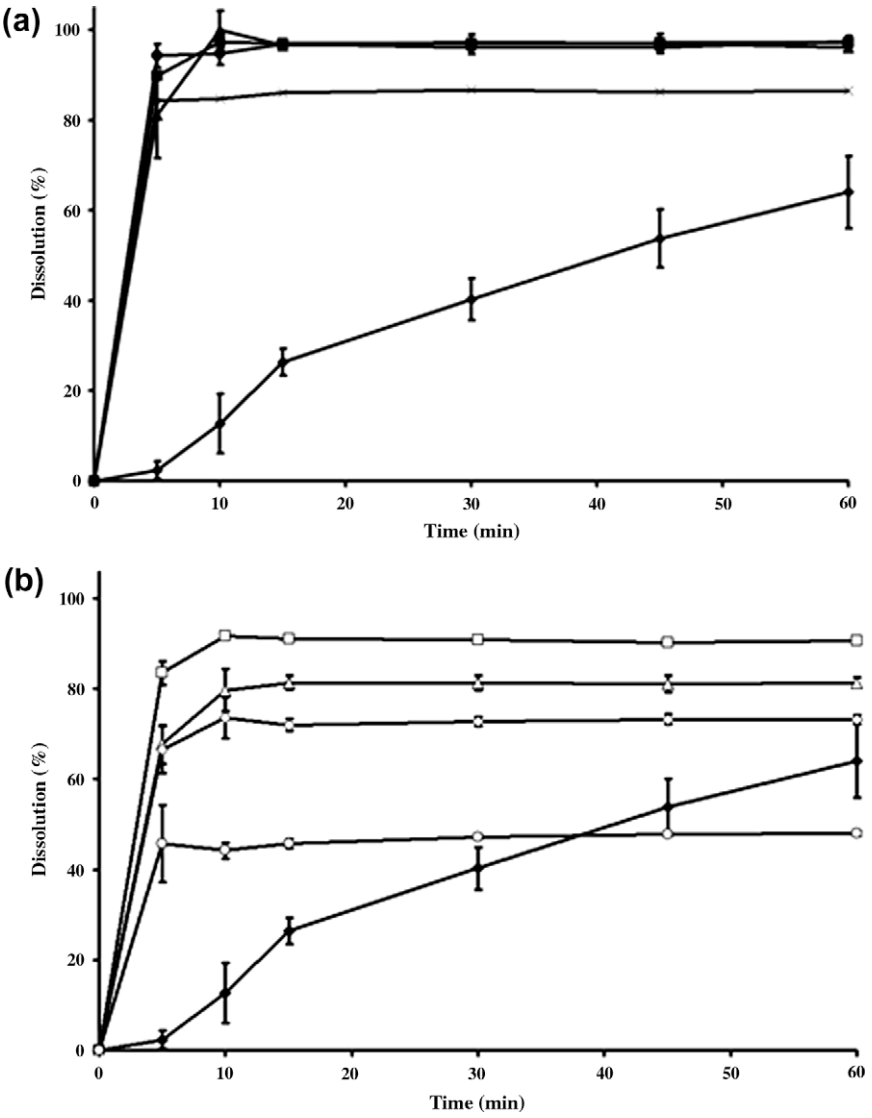

Fig. 9. Dissolution profiles of HCT solid dispersions prepared by KSD and HME for compositions containing PVPVA 64 (a) and HPMC E3 (b) Key: HCT – Crystalline (♦), HCT:PVPVA 64, KSD, 160 °C (■), HCT:PVPVA 64, HME, 160 °C (▲), HCT:PVPVA 64, HME, 180 °C (●), HCT:PVPVA 64, HME, 200 °C, Recirculation = 5 min (X), HCT:HPMC E3, KSD, 160 °C (□), HCT:HPMC E3, KSD, 180 °C (Δ), HCT:HPMC E3, HME, 180 °C (◇), HCT:HPMC E3, HME, 200 °C (○) Each vessel ($n = 3$) contained 25.0 mg of HCT theoretical equivalent without adjustment for assay and was conducted in 900 ml of 0.1 N HCl at a paddle speed of 50 rpm using USP Apparatus II.

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