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An Investigation into the Dissolution Properties of Celecoxib Melt Extrudates: Understanding the Role of Polymer Type and Concentration in Stabilizing Supersaturated Drug Concentrations

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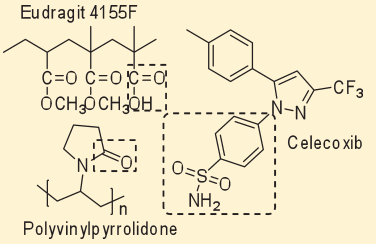
ABSTRACT: In this study, the dissolution properties of celecoxib (CX) solid dispersions manufactured from Eudragit 4155F and polyvinylpyrrolidone (PVP) were evaluated. Hot-melt extrusion (HME) technology was used to prepare amorphous solid dispersions of drug/polymer binary systems at different mass ratios. The drug concentrations achieved from the dissolution of PVP and Eudragit 4155F solid dispersions in phosphate buffer, pH 7.4 (PBS 7.4) were significantly greater than the equilibrium solubility of CX (1.58 μg/mL). The degree of supersaturation increased significantly as the polymer concentration within the solid dispersion increased. The maximum drug concentration achieved by PVP solid dispersions did not significantly exceed the apparent solubility of amorphous CX. The predominant mechanism for achieving supersaturated CX concentrations in PBS 7.4 was attributed to stabilization of amorphous CX during dissolution. Conversely, Eudragit 4155F solid dispersions showed significantly greater supersaturated drug solutions particularly at high polymer concentrations. For example, at a drug/polymer ratio of 1:9, a concentration of 100 μg/mL was achieved after 60 min that was stable (no evidence of drug recrystallization) for up to 72 h. This clearly identifies the potential of Eudragit 4155F to act as a solubilizing agent for CX. These findings were in good agreement with the results from solubility performed using PBS 7.4 in which Eudragit 4155F had been predissolved. In these tests, Eudragit 4155F significantly increased the equilibrium solubility of CX. Solution ^{1}H NMR spectra were used to identify drug/polymer interactions. Deshielding of CX aromatic protons (H-1a and H-1b) containing the sulfonamide group occurred as a result of dissolution of Eudragit 4155F solid dispersions, whereas deshielding of H-1a protons and shielding of H-1b protons occurred as a result of the dissolution of PVP solid dispersions. In principle, it is reasonable to suggest that the different drug/polymer interactions observed give rise to the variation in dissolution observed for the two polymer/drug systems.



KEYWORDS: hot-melt extrusion, amorphous drugs, solid dispersions, supersaturated solutions, drug/polymer interactions

INTRODUCTION

Over the past decade amorphous drug forms have received considerable attention due to the increased solubility they exhibit relative to their crystalline counterparts.[1,2] In particular, the generation of amorphous drug forms using solid dispersions is highly attractive for enhancing the dissolution rate of poorly soluble drugs.[3,4] Several research groups have demonstrated the viability of hot-melt extrusion (HME) in manufacturing amorphous solid dispersions.[5−7] HME is a solvent-free technique, and processing times, often less than 2 min, making this technology more attractive than other traditional methods used to prepare solid dispersions, e.g., solvent evaporation methods and other hot methods.[8,9]

The pharmaceutical advantage of amorphous drugs is compromised by their poor thermodynamic stability and their tendency to recrystallize rapidly in the solid state or during dissolution.[2,3] Although often difficult to achieve, through the careful selection of suitable polymeric carriers, amorphous solid dispersions may be stabilized through formation of secondary drug/polymer interactions[10−12] or/and by their antiplasticization effects, which can result in reducing their molecular mobility.[13] Therefore, the rational use of polymers in formulating acceptable solid dispersions is paramount in stabilizing amorphous drugs.

To achieve the full benefit of amorphous solid dispersions, it is necessary not only to stabilize the drug during storage but also to maintain supersaturated concentration of drug during dissolution. Polymers used to manufacture amorphous solid dispersions have previously been shown to function as stabilizing agents and thus maintain supersaturated concentrations achieved during dissolution of amorphous drugs.[14] Additionally, amorphous solid dispersions may generate higher solution concentrations than those achieved with the pure amorphous drug,[15] suggesting that certain polymers may act as solubilizing agents through complex formation with the drug during dissolution.[16,17]

The effect of polymeric carriers in stabilizing the dissolution of amorphous drug dispersions has received considerable attention. It has been reported that itraconazole solid dispersions manufactured from blends of Eudragit EPO and PVP/VA64 provided improved stability during dissolution in comparison to Eudragit EPO alone.[18] In another study, the addition of Carbopol 974P to itraconazole/Eudragit L100-55 solid dispersions prolonged

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supersaturation of the drug, significantly improving itraconazole absorption.[19] Recently, the addition of minor amounts of Eudragit NE to felodipine/Eudragit E100 solid dispersions significantly maintained supersaturated drug levels.[20]

Although there has been a significant volume of work conducted that has investigated the dissolution behavior of amorphous solid dispersions and role polymers play in stabilizing supersaturated drug concentrations, the mechanism of stabilization is still not well understood.[21] In this study, we have used solution ^{1}H NMR to provide a more fundamental understanding of the role drug−polymer interactions have in maintaining supersaturated drug concentrations during dissolution of amorphous solid dispersions.

Celecoxib (CX) is a poorly soluble drug that can be used for chemoprevention of colorectal cancer. Delivery of this active to the colon is not only challenging in terms of targeting the desired gastrointestinal (GI) region but additionally due to the lower motility, limited fluid content and the higher fluid viscosity relative to the upper sections of GI tract.[22] These conditions in the colon may be problematic in terms of solubilization especially for poorly soluble drugs delivered for the local treatment of colonic diseases. Solubilization problems may significantly affect the therapeutic and clinical performance of these drugs. Consequently there is a need to deliver these drugs in formulations that can increase their solubility in colonic fluid and hence improve therapeutic response.[23]

Eudragit 4155F is a freeze-dried product of Eudragit FS 30 D. It is a copolymer of methyl acrylate, methyl methacrylate and methacrylic acid. The ratio of the free carboxyl groups to the ester groups is approximately 1:10. Eudragit 4155F is a pH-dependent anionic copolymer that dissolves at pH >7.0. This polymer therefore may provide a suitable platform for the delivery of CX to the colon while also improving the inherent solubility of the drug if formulated as a solid dispersion. Although there are a number of articles describing the dissolution enhancement of CX, there are currently no articles describing the dissolution properties of Eudragit 4155F solid dispersions. In this study, the ability of Eudragit 4155F to enhance the dissolution properties of amorphous CX have been investigated, and compared with PVP solid dispersions. The *in vitro* dissolution studies were carried out under nonsink conditions in order to evaluate the ability of the polymer to generate and maintain supersaturated drug solutions. Additionally, solution ^{1}H NMR spectroscopic studies were conducted in order to investigate drug/polymer interactions and in order to better understand the mechanisms involved during dissolution of CX from the dispersions.

MATERIALS

Celecoxib (CX) was a kind gift from Hikma Pharmaceuticals Co. (Amman, Jordan). Eudragit 4155F (MW = 135,000 g/mol) was donated by Evonik Röhm GmbH (Darmstadt, Germany). Polyvinylpyrrolidone K25 (MW = 24,000 g/mol) (PVP K25) was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany). All other chemicals used were of analytical grade or equivalent quality.

METHODS

Preparation of Melt Extrudates. CX was mixed with PVP or Eudragit 4155F at drug/polymer mass ratios of 1:9, 3:7, 1:1, and 7:3 using a mortar and pestle for 2 min. The prepared physical mixtures (PMs) were extruded using a corotating twin-screw extruder (Minilab, Thermo Electron Corporation, Germany) at a screw speed of 100 rpm. CX/Eudragit mixtures were extruded at a temperature of 170 °C. CX/PVP physical mixtures containing 1:1 and 7:3 ratios were extruded at a temperature of 150 °C, whereas the 3:7 ratio was extruded at 170 °C. The melt extrudates were ground using a mortar and pestle, passed through a 355 μm sieve, transferred to open glass vials and stored in a desiccator over silica at 20 °C. A suitable quantity of the physical mixture from each drug loading was kept for analysis.

Preparation of an Amorphous CX/Eudragit 4155F Physical Mixture. Amorphous CX was prepared by heating CX to 170 °C for 2 min using a stainless steel beaker followed by quench cooling in an ice bath. The prepared amorphous CX was subsequently mixed with Eudragit 4155F at a drug/polymer mass ratio of 1:9 using a mortar and pestle.

Thermogravimetric Analysis (TGA). The thermal stability of CX, PVP and Eudragit 4155F was assessed using a TA Instruments Q500 TGA (Leatherhead, U.K.). Ramp tests were performed at a scan speed of 10 °C/min over a range from 20 to 500 °C. Nitrogen was used as the purging gas during all TGA experiments. All analyses were performed in triplicate.

Differential Scanning Calorimetry (DSC). DSC analyses were conducted using a TA Instruments Q100 DSC (Leatherhead, U.K.) equipped with a refrigerated cooling system. All data analyses were performed using Universal Analysis 2000 software. Samples between 5.0 and 10.0 mg were accurately weighed and placed into crimped aluminum pans. The DSC was calibrated for baseline correction using empty pans, and for temperature/enthalpy using indium. Nitrogen was used as the purging gas at a flow rate of 50 mL/min. All analyses were performed at least in triplicate.

Powder X-ray Diffractometry (PXRD). PXRD patterns were obtained using a Philips X'Pert PRO diffractometer with a PW3040 generator (Philips, Almelo, The Netherlands) with X'Pert Data Viewer version 1.0 software. Samples were placed on a zero background sample holder and incorporated onto a spinner stage. Cu Kα_1 radiation was used as an X-ray source. Soller slits (0.04 rad) were used for the incident and diffracted beam path. The angular range (3−60 2θ) was scanned in continuous mode with a step size of 0.0167°, a time per step of 50 s and a scan speed 0.024°/min. The diffraction pattern was measured using a voltage of 40 kV and a current of 40 mA. All analyses were performed in triplicate.

The Effect of Polymer Type on the Solubility of CX. The equilibrium solubility of crystalline CX was measured at 37° ± 0.2 °C using phosphate buffer (pH 7.4) (PBS 7.4) in the presence or absence of the polymer. 50 mg of crystalline CX was dispersed in 500 mL of PBS 7.4, in which 500 and 1000 mg of polymer (PVP or Eudragit 4155F) had been previously dissolved, leading to a final polymer concentration of 1.0 and 2.0 mg/mL. The solution was stirred with a rotating paddle at 100 rpm. Samples of 5 mL were withdrawn from each vessel at predetermined time intervals (24, 48, and 72 h) and filtered through a cellulose acetate filter (0.45 μm, Nalgene Labware, Rochester, NY, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd., Oxford, U.K.) UV−Vis spectrophotometer at 250 nm and a standard calibration curve that was linear over the concentration range (2.5−20 μg/mL). No interference from the PVP or Eudragit 4155F on the CX assay was observed at 250 nm. The

Table 1. Equilibrium Solubility of Celecoxib (CX) in PBS pH 7.4 with or without Dissolved Polymer at 37 ± 0.2 °C

added polymer (mg/mL)	equilibrium solubility of celecoxib (CX) in pH 7.4 (μg/mL)
without polymer	1.58 (0.04)[a]
PVP	
1.0	1.57 (0.03)
2.0	1.59 (0.03)
Eudragit 4155F	
1.0	2.08 (0.09)
2.0	4.12 (0.08)

[a] Values in parentheses represent the standard deviations, $n = 3$.

solubility of CX in PBS 7.4 in the absence of polymer was also evaluated. All measurements were carried out in triplicate.

The Inhibition of CX Recrystallization from Supersaturated Solutions. A concentrated solution of CX in methanol was prepared by dissolving 25 mg of crystalline CX in 5 mL methanol which was subsequently added to 500 mL of PBS 7.4 at a temperature of 37 ± 0.2 °C. This generated an initial drug solution concentration of 50 μg/mL in PBS 7.4, into which 500, 117, 50, or 20 mg of polymer (PVP or Eudragit 4155F) had been previously dissolved, leading to a final polymer concentration of 1000, 234, 100, or 43 μg/mL, respectively. The solution was stirred with a rotating paddle at 100 rpm. 5 mL samples were withdrawn from each vessel at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360 min) and filtered through a cellulose acetate filter (0.45 μm, Nalgene Labware, Rochester, NY, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd., Oxford, U.K.) UV−vis spectrophotometer at 250 nm and a standard calibration curve. The percent of CX dissolved ($n = 3$) was plotted as a function of time. The same experiments were performed in PBS 7.4 in the absence of any polymer.

***In Vitro* Dissolution Studies.** The *in vitro* drug dissolution properties of solid dispersions and physical mixtures were examined according to the USP paddle method (USP 30, 2007). Samples equivalent to 50 mg of CX were added to 500 mL of PBS 7.4 at a temperature of 37 ± 0.2 °C. The solution was stirred with a rotating paddle at 100 rpm. Samples of 5 mL were withdrawn from each vessel at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, 120, 180, 240, 300, 360, 1440 (24 h), 2880 (48 h), and 4320 min (72 h)). All samples taken were filtered through a cellulose acetate filter (0.45 μm, Nalgene Labware, Rochester, NY, USA). At each time point the same volume of fresh medium was replaced. The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd., Oxford, U.K.) UV−Vis spectrophotometer at 250 nm and a standard calibration curve. The percent of CX dissolved for each formula ($n = 3$) was plotted as a function of dissolution time. In addition to the test fluid of pH 7.4, similar experiments were performed on Eudragit 4155F solid dispersions using a test fluid of pH 9.4. This was solely to better understand the mechanism of release and was not intended to represent biological release media.

Solution ^{1}H NMR. ^{1}H NMR spectra were recorded on a Bruker DRX spectrometer (Switzerland) operating at 500.13 MHz, using a 5 mm multinuclear probe with $\pi/2$ pulses of 6.0 μs. The measurements were performed at 27 °C in deuterated chloroform ($CDCl_3$) using tetramethylsilane (TMS) as an internal standard. All analyses were carried out in triplicate.

Statistical Analysis. The effect of formulation on drug solubility/dissolution properties were statistically analyzed using a repeated measures one-way ANOVA. Individual differences in drug dissolution between formulations were statistically identified using Fisher's PLSD test. In all cases $p < 0.05$ denoted significance.

RESULTS AND DISCUSSION

Thermal Stability of CX Polymeric Excipients. TGA is a very rapid analytical technique that can determine mass loss as a function of temperature. Consequently, TGA has often been used to assess the thermal stability of materials prior to HME.[24,25] The thermal stability of CX at a temperature of 170 °C has been confirmed previously using TGA isothermal experiments.[26] In a standard TGA ramp test, CX did not exhibit any volatile degradation prior to reaching 250 °C, after which significant mass loss was detected (data not shown). Additionally, TGA ramp tests confirmed the thermal stability of PVP and Eudragit 4155F at the extrusion temperatures used. It has been previously reported that approximately 6% mass loss is observed for PVP samples at temperatures below 100 °C. This has been attributed to loss of free water.[12]

Equilibrium Solubility in the Presence of Polymeric Components. The solubility of the drug in the presence of concentrated solutions of a polymeric carrier can help determine the mechanism of dissolution from a solid dispersion.[27] To examine the solubilizing power of PVP and Eudragit 4155F, the equilibrium solubility of crystalline CX in PBS 7.4 containing 1.0 and 2.0 mg/mL of each of the respective polymers was determined and compared to the equilibrium solubility in PBS 7.4 in the absence of polymer. Polymer concentrations of 1.0 and 2.0 mg/mL were selected as they represented conditions wherein it would be most likely to enhance solubility (high polymer to drug ratio). In addition, a polymer concentration of 1.0 mg/mL represents the concentration of polymer that would be achieved in solution following dissolution of a drug/polymer matrix at a ratio of 1:9. All solutions reached equilibrium after 48 h. As shown in Table 1, the equilibrium solubility of CX did not change significantly when PVP was present in PBS 7.4 at 1.0 and 2.0 mg/mL ($p = 0.7759$), while there was a significant increase ($p < 0.0001$) in the equilibrium solubility of CX when Eudragit 4155F was present at 1.0 mg/mL (1.32-fold) and 2.0 mg/mL (2.63-fold). These results indicate that Eudragit 4155F has a solubilizing effect on CX, whereas PVP has no such effect. It has been reported in previous studies that the solubility of poorly soluble drugs was enhanced significantly in aqueous solutions in which hydrophilic carriers had been dissolved as a result of the formation of weakly soluble complexes. For example, the solubility of rofecoxib and ibuproxam was enhanced in the presence of aqueous PVP and PEG solutions.[28,29]

Inhibition of Recrystallization from Supersaturated Solutions. The ability of PVP and Eudragit 4155F to inhibit crystallization of CX from a supersaturated solution was evaluated by adding a concentrated solution of CX to PBS 7.4, in which the polymers had been predissolved while monitoring the solution concentration as a function of time. Figures 1 and 2 show results obtained at different polymer solution concentrations, 1000, 234, 100, and 43 μg/mL, which correspond to the polymer solution concentrations that would be produced by total dissolution of

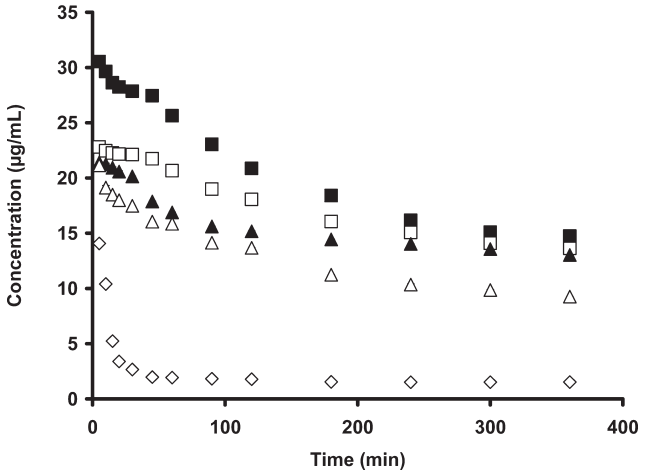

Figure 1. Inhibitory effects of PVP on recrystallization of a supersaturated solution of celecoxib (CX) (50 μg/mL) at PBS pH 7.4 containing 1000 (■), 234 (□), 100 (▲), 43 (Δ) (μg/mL) of PVP and in the absence of any polymer(s) (◇). The data shown is the average of three replicates, and in all cases the COV was <6.

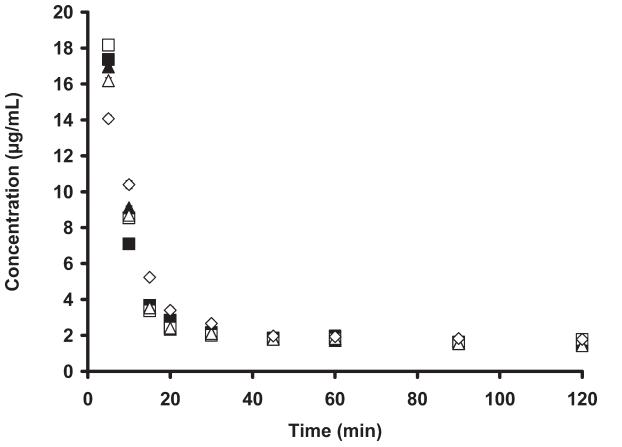

Figure 2. Inhibitory effects of Eudragit 4155F on recrystallization of a supersaturated solution of celecoxib (CX) (50 μg/mL) at PBS pH 7.4 containing 1000 (■), 234 (□), 100 (▲), 43 (Δ) (μg/mL) of Eudragit 4155F and in the absence of any polymer(s) (◇). The data shown is the average of three replicates, and in all cases the COV was <6.

solid dispersions at drug/polymer ratios of 1:9, 3:7, 1:1 and 7:3, respectively. The results obtained for PBS 7.4 without any polymer dissolved are shown for reference. PVP concentration of 1000 μg/mL was tested just for comparison and does not correspond to any of the prepared solid dispersions as CX/PVP physical mixture at drug/polymer ratio of 1:9 could not be extruded without the addition of a plasticizer given that plasticizer inclusion may affect storage stability (through T_g reduction) and/or the drug release properties (plasticizer solubility).

The initial solution concentration of CX that was generated by dilution of the concentrated methanol drug solution was 50 μg/mL. As shown in Figure 1, in the absence of polymer, the CX concentration decreased rapidly, reaching 14.07 ± 0.19 μg/mL after 5 min, and then continued to decrease until achieving a plateau after 45 min with a concentration close to the equilibrium solubility of crystalline CX. This rapid decrease in CX concentration suggested that CX recrystallized from a supersaturated concentration immediately. These results are in good agreement with data presented by Konno et al.,[21] wherein felodipine rapidly recrystallized in the absence of polymeric excipients.

Interestingly, in the presence of PVP (Figure 1), the initial drug concentration, measured 5 min after addition of a concentrated solution of CX, was significantly higher in PBS 7.4 containing 1000 μg/mL of PVP than other lower concentrations ($p < 0.0001$). Moreover, significant differences were observed between the CX concentrations achieved after 5 min in PBS 7.4 containing 243 μg/mL and the other lower PVP concentrations 100 μg/mL ($p = 0.0042$) and 43 μg/mL ($p = 0.0015$). Conversely, there was no significant difference between the drug concentrations achieved in PBS 7.4 containing PVP concentrations of 100 and 43 μg/mL ($p = 0.5413$). The initial CX concentration measured after 5 min was 30.54 ± 0.09 μg/mL, for 1000 μg/mL PVP concentration, whereas it was 22.8 ± 0.13, 21.41 ± 0.06 and 21.15 ± 0.13 μg/mL for PVP concentrations of 234, 100, and 43 μg/mL, respectively. These results indicate that there was a highly significant recrystallization inhibition due to the presence of PVP at all concentrations relative to PBS 7.4 in which no polymer had been dissolved ($p < 0.0001$ in all cases). After 6 h, CX reached concentrations of 14.75 ± 0.26, 13.63 ± 0.15, 13.03 ± 0.15 and 9.27 ± 0.07 μg/mL in PBS 7.4 in which PVP was present at concentrations of 1000, 234, 100, and 43 μg/mL, respectively. Differences in drug concentration were still apparent after a 6 h period and were also a function of PVP concentration. Similarly, the inhibition of RS-8359 (a water-insoluble drug) recrystallization from a supersaturated drug concentration was dependent upon the HPMC, HPC and PVP polymer concentration in phosphate buffer.[17] Precipitation rate decreased with increasing polymer concentration. The achieved CX concentrations after 6 h were significantly higher than the equilibrium solubility of crystalline CX (1.58 μg/mL) ($p < 0.0001$ in all cases), indicating the ability of PVP, across all concentrations, to maintain supersaturated levels of CX.

In contrast to PVP, dispersion of Eudragit 4155F in PBS 7.4, in general, did not inhibit recrystallization of CX from supersaturated concentration (Figure 2). The concentration of CX remaining in solution, 5 min after addition of a supersaturated concentration of the drug, was significantly higher for solutions containing 4155F than buffer containing no polymer ($p < 0.0001$). These differences may be attributed to viscosity effects, and the increase in the fluid viscosity surrounding solubilized drug, resulting in retardation of CX recrystallization.[17] After this initial period (5 min), the concentration of CX remaining in solution rapidly decreased until a drug concentration plateau was achieved (~45 minutes); drug concentration approximated to the equilibrium solubility of crystalline CX (Figure 2). Comparison of the inhibitory effects of PVP and 4155F suggests that PVP was more efficient in stabilizing CX once a supersaturated concentration was achieved. Eudragit 4155F did not show any considerable stabilization effect but was shown to be useful in enhancing drug solubility. Interestingly, in a previously published paper, Albers et al.[30] have shown that Eudragit EPO polymer can be used to significantly increase the dissolution of CX when formulated as a molecular dispersion. Interestingly, and in a similar fashion to Eudragit 4155F, EPO was not capable of inhibiting recrystallization (recrystallized <10 min) of CX from a supersaturated concentration. The diversity of the 4155F and PVP dissolution/solubility data confirm the current status of the field; the mechanisms driving stabilization of concentrated drug

Table 2. Solubility of Various Formulations of Celecoxib (CX)/Polymer Binary System in BPS pH 7.4 after 24, 48, and 72 h at 37 ± 0.2 °C[a]

		CX concn in PBS pH 7.4 (μg/mL)		
formulation	T_g (°C)	24 h	48 h	72 h
Formulation Containing PVP (Drug:Polymer)				
(3:7) PM		1.28 (0.09)	1.62 (0.08)	1.64 (0.11)
(1:1) PM		1.32 (0.08)	1.58 (0.12)	1.62 (0.09)
(7:3) PM		0.94 (0.05)	1.56 (0.07)	1.59 (0.08)
(3:7) SD	130.70 (1.70)	21.36 (0.14)	21.69 (0.14)	21.92 (0.07)
(1:1) SD	112.30 (0.70)	14.37 (0.7)	13.91 (0.5)	13.61 (0.5)
(7:3) SD	88.40 (0.90)	8.23 (0.06)	7.82 (0.09)	7.41(0.08)
Formulation Containing Eudragit 4155F (Drug:Polymer)				
(1:9) PM		62.33 (1.24)	63.56 (1.35)	64.25 (1.04)
(3:7) PM		6.67 (0.20)	7.01 (0.04)	7.04 (0.02)
(1:1) PM		3.04 (0.02)	4.88 (0.09)	5.05 (0.03)
(7:3) PM		1.60 (0.07)	2.46 (0.01)	2.47 (0.01)
(1:9) SD	51.30 (0.56)	100.73 (0.14)	100.59 (0.31)	100.67 (0.30)
(3:7) SD	52.70 (0.42)	71.61 (0.32)	56.09 (0.19)	53.37 (0.28)
(1:1) SD	55.10 (0.15)	12.30 (0.30)	13.24 (0.21)	10.96 (0.16)
(7:3) SD	59.20 (0.22)	4.77 (0.02)	4.67 (0.04)	4.65 (0.04)

[a] Values in parentheses represent the standard deviations. n = 3. PM denotes the physical mixtures containing crystalline CX.

solutions (supersaturated) in the presence of polymeric materials, and the solubilizing action of polymers, remain poorly understood.[21] Previously published articles suggest fluid viscosity and drug/polymer interactions as possible contributing factors.[17] Furthermore, alteration of crystal growth and, in particular, the influence of dispersed polymers on crystal habit has been suggested as a possible reason. In this respect, changes in crystal habit were attributed to adhesion of polymer to the growing plane of the drug crystal.[17] In a further study, conducted to examine the efficiency of different polymers to maintain supersaturated levels of felodipine, the mechanistic reason for the superior performance of hydroxypropylmethylcellulose acetate succinate (HPMCAS), compared with hydroxypropylmethyl cellulose (HPMC) and PVP, remains unclear.[21] Furthermore, Eudragit E100 was shown to be the most efficient polymer at inhibiting the crystallization of UC 781, an anti-HIV drug, from supersaturated levels generated from concentrated methanol drug solutions.[31] The stabilizing effect of Eudragit E100 was concentration dependent.

Prediction of Apparent Solubility. Due to physical instability (recrystallization) during dissolution, it is difficult to measure experimentally the practical solubility of amorphous materials.[32] A model developed by Parks et al.[33,34] may be used to predict the relative solubility of the amorphous and crystalline forms of CX based on the difference in their free energy (ΔG). Using eq 1 the solubility ratio ($S_{amorphous}/S_{crystalline}$) of the two forms at a certain temperature is directly related to the free energy difference (ΔG) between these two forms.

$$\Delta G = RT\ ln\ \frac{S_{amorphous}}{S_{crystalline}} \quad (1)$$

R is the gas constant, T is the temperature, and S is the solubility.

The Hoffman equation can be used to estimate the free energy difference between the amorphous and crystalline forms if the melting temperature (T_m) and the heat of fusion (ΔH_f) of the crystalline form are known, as shown in eq 2.

$$\Delta G = \frac{\Delta H_f (T_m - T)T}{{T_m}^2} \quad (2)$$

The Hoffman equation was used successfully by Marsac et al.[35] to provide reasonable estimate of the free energy difference between amorphous and crystalline felodipine. Using eq 2 and at conditions where $T_m \gg T$, it can be deduced that the higher the melting point and heat of fusion of a compound, the greater the solubility enhancement that may be achieved through utilization of an amorphous drug form. Additionally, there are other factors that will affect the experimental solubility, such as the stability of the amorphous drug forms in the dissolution medium, its glass transition temperature (T_g), particle size and interactions with the polymer in solid state and in solution.[15,36] While the above approach is approximate, it does provide a useful guide as to the solubility enhancement that may be achieved through generation of amorphous drug.

By applying eqs 1 and 2, the solubility ratio of the amorphous and crystalline forms of CX at pH 7.4 and at 37 °C was predicted to be approximately 12, which means that the theoretical solubility of amorphous CX is 12 times that of crystalline CX. The equilibrium solubility of crystalline CX was 1.58 (μg/mL) (Table 1), so the apparent solubility of amorphous CX was estimated to be 19.0 (μg/mL).

Solid State Properties of Melt Extrudates. PXRD pattern of crystalline CX showed distinct crystal peaks at 2θ angles of 15.0, 16.0, 19.6, 21.5, 22.3, 23.4, 25.3, and 29.4°. The X-ray pattern of CX/PVP and CX/Eudragit 4155F physical mixtures (1:9), the lowest drug loading, showed the characteristic peaks of crystalline CX albeit with lower intensities. No CX crystal peaks were detected in the PXRD spectra of the melt extrudates. The DSC thermogram of crystalline CX showed a sharp endotherm at 163.2 ± 0.9 °C, corresponding to melting of CX. Interestingly, this melting endotherm has not been detected in the melt extrudates, although it was possible to detect it in the drug/polymer physical mixtures (1:9) ratio. Additionally, the DSC thermograms of the melt extrudates exhibited a single T_g (Table 2).[26] These PXRD and DSC results confirmed the formation of amorphous solid dispersions (solid molecular dispersions) within CX/PVP and CX/Eudragit 4155F binary systems after HME.

***In Vitro* Dissolution of Drug/Polymer Dispersions.** *CX/PVP Solid Dispersion.* Table 2 shows the CX concentrations (μg/mL) generated from CX/PVP and CX/Eudragit 4155F solid dispersions and physical mixtures after 24, 48, and 72 h. Dissolution from PVP solid dispersions resulted in higher solution concentrations than the equilibrium solubility of crystalline CX (1.58 μg/mL), indicating that supersaturated solutions were generated. As shown in Figure 3 supersaturated levels of CX were observed that increased with increasing polymer load in the solid dispersion. The drug dissolution profiles from PVP solid dispersions at a drug/polymer ratio of 3:7 obtained a concentration of 20.52 ± 0.13 μg/mL after 5 h that remained stable for up to 72 h achieving a final concentration of 21.46 ± 0.35 μg/mL (Table 2). The stabilized solution concentrations of CX were close to the theoretical solubility of amorphous CX (19.0 μg/mL), predicted from eq 1. This suggests that PVP at a loading of 70% (w/w) results in dissolution of CX up to a level consistent with the amorphous solubility of the drug and that recrystallization is

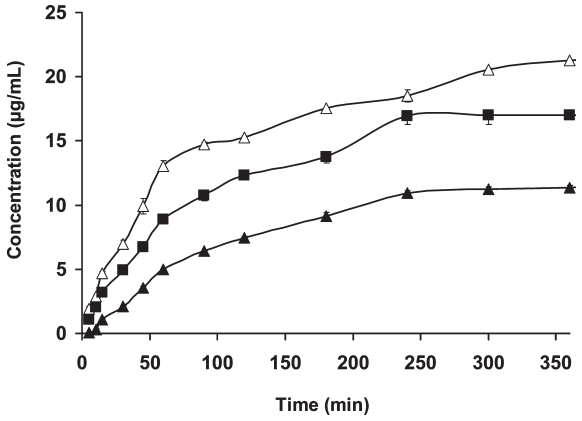

Figure 3. Dissolution profiles of celecoxib (CX) (100 μg/mL) from CX/PVP solid dispersions: 3:7 (△), 1:1 (■) and 7:3 (▲) in PBS 7.4. The data shown is the average of three replicates and in all cases the COV was <8.

inhibited. Interestingly, the mass of formulation added to the dissolution vessel reflected a CX concentration of 100 μg/mL. Therefore even at a 70% PVP loading we only observe 20% (20 μg/mL) drug solubility from the matrix. This is significantly higher than the solubility of crystalline CX. The drug solution concentrations from dissolution of amorphous solid dispersions containing 50% (w/w) PVP achieved a plateau after 5 h with a drug concentration of 17.03 ± 0.21 μg/mL. Thereafter a decrease in drug concentration was observed as a result of recrystallization with a concentration of 13.61 ± 0.46 μg/mL being achieved after 72 h. CX/PVP amorphous solid dispersions containing drug:polymer ratio of 7:3 achieved a plateau after 4 h with a drug concentration of 10.93 ± 0.17 μg/mL. Again a small but significant decrease of drug concentration was observed (7.41 ± 0.08 μg/mL) after 72 h as a result of CX recrystallization. These dissolution results indicate that PVP solid dispersions at all concentrations maintained supersaturated levels of CX achieving drug concentrations significantly higher than the equilibrium solubility of crystalline CX (1.58 μg/mL) for the whole period of the dissolution study (72 h) ($p < 0.0001$ in all cases). The results obtained suggest that PVP is highly efficient in promoting and stabilizing the dissolution of CX. There was no significant difference in the equilibrium solubility of CX obtained from the physically mixed samples of crystalline CX with PVP at 3:7 ($p = 0.4248$), 1:1 ($p = 0.5206$) and 7:3 ($p = 0.8559$) ratios compared to crystalline CX (Table 2). This suggests that PVP has no solubilization effect, and substantiates our hypothesis that supersaturated levels of drug in the presence of PVP are related to amorphous solubility and stabilization of the drug by PVP. These results were in agreement with the results obtained from experiments examining the inhibitory effects of PVP against CX crystallization from supersaturated solutions.

It was reported by Gupta et al.[15] that amorphous CX recrystallizes so rapidly during dissolution in water that concentrations approximately equal to the equilibrium solubility of crystalline CX are achieved. The rapid recrystallization of amorphous CX during dissolution may be attributed to the powerful plasticization effect by water molecules once amorphous CX contacts the aqueous dissolution media, particularly given the low T_g values of amorphous CX. PVP has a high T_g value (154.6 ± 0.7 °C),[12] and because of the miscibility with CX, solid molecular dispersions (single phase) exhibit a single T_g between the T_g of the two components.[37] The increased T_g of the solid molecular dispersions may result in greater physical stability during dissolution.[15] Thus the greater supersaturated levels generated for CX with increasing PVP concentration may be attributed to increased stabilization during dissolution due to the higher T_g values for CX/PVP systems at elevated PVP concentrations (Table 2). This antiplasticization effect by PVP on amorphous CX may enable CX to stay in an amorphous form for longer periods of time especially given that it is in immediate contact with PVP during dissolution. Thus intimate contact between CX and PVP achievable in solid molecular dispersions, formed using HME, results in supersaturated levels of CX.[15,21]

CX/Eudragit Solid Dispersion. The CX concentrations achieved from Eudragit 4155F solid dispersions in PBS 7.4 after 72 h were significantly higher than the equilibrium solubility of crystalline CX (1.58 ± 0.04 μg/mL) ($p < 0.0001$ in all cases), indicating that supersaturated levels of CX were generated and maintained for up to 72 h at all drug/polymer ratios (Table 2). The supersaturated levels generated by dissolution of the amorphous solid dispersions were mostly attributed to the solubilization ability of Eudragit 4155F. The CX drug concentrations achieved at drug to polymer ratios of 1:9 and 3:7 ratios after 72 h (100.67 ± 0.3 and 53.37 ± 0.3 μg/mL, respectively) far exceeded the theoretical solubility of amorphous CX (19 μg/mL). The solubilizing effect of Eudragit 4155F was shown previously by the significant increase in the equilibrium solubility of crystalline CX in PBS 7.4 in which Eudragit 4155F had been predissolved at concentrations of 1.0 and 2.0 mg/mL (Table 1). This solubilizing effect was further confirmed by the significant increase in the equilibrium solubility of CX achieved from physically mixed samples containing crystalline CX (Table 2) ($p < 0.0001$ in all cases). The equilibrium solubility of crystalline CX increased with increasing polymer concentration in the physical mixtures, indicating the ability of Eudragit 4155F to act as an efficient solubilizer for CX. The equilibrium solubility of crystalline CX in PBS 7.4 achieved from the physically mixed samples at drug/polymer weight ratio of 1:9 (polymer concentration of 1.0 mg/mL) was 31.0- and 15.5-fold greater than the equilibrium solubility achieved from the PBS 7.4 in which Eudragit 4155F had been previously dissolved at a polymer concentration of 1.0 and 2.0 mg/mL, respectively. These results may be attributed to the increased contact of CX with Eudragit 4155F during dissolution from the physical mixture samples, enhancing the solubilizing effect of the polymer. Moreover, the dissolution properties of CX were further increased from solid dispersions of Eudragit 4155F in comparison to the corresponding physical mixture samples (Table 2). One reason for the disparity between the equilibrium solubility values and the drug concentration achieved from solid dispersions and physically mixed samples may be due to a difference in dissolution environment of the drug in both cases. In experiments wherein the polymer is dispersing in the release media at the same time as the drug, the drug may become incorporated in a concentration polymer-rich diffusion layer increasing the dissolution performance. Most certainly, within molecular dispersions, the drug release properties are governed by the properties of the polymer. In physically mixed samples it is not unreasonable to suggest that polymer disperses more rapidly than drug and encapsulates the drug facilitating dissolution. Within molecular dispersions, improvement in drug dissolution can also be attributed to the intimate contact between CX and Eudragit 4155F during HME resulting in greater enhancement of CX dissolution. As shown in

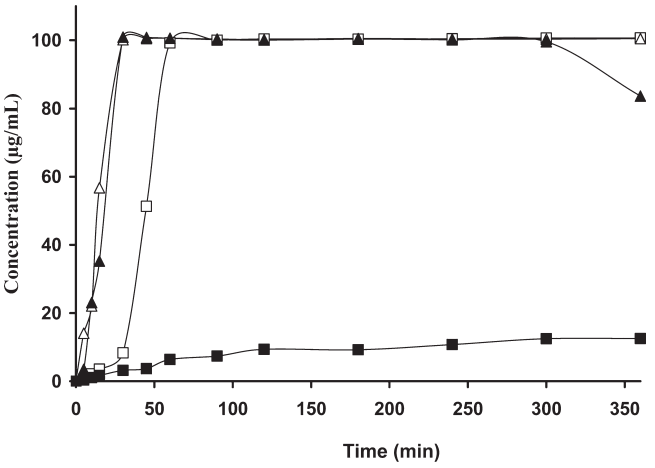

Figure 4. Dissolution profiles of celecoxib (CX) (100 μg/mL) from CX/Eudragit 4155F solid dispersions at different pHs: 1:9 pH 7.4 (△), 1:9 pH 9.4 (▲), 3:7 pH 7.4 (■), 3:7 pH 9.4. (□). The data shown is the average of three replicates, and in all cases the COV was <8.

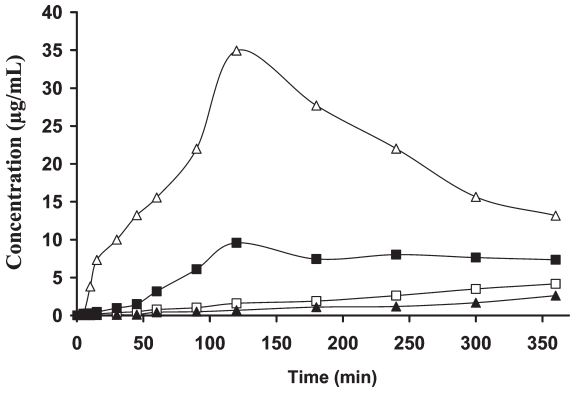

Figure 5. Dissolution profiles of celecoxib (CX) (100 μg/mL) from CX/Eudragit 4155F solid dispersions at different pHs: 1:1 pH 7.4 (□), 1:1 pH 9.4 (△), 7:3 pH 7.4 (▲), 7:3 pH 9.4 (■). The data shown is the average of three replicates, and in all cases the COV was <8.

Figure 4, drug release properties of CX from Eudragit 4155F solid molecular dispersions were highly dependent on the amount of polymer in the solid dispersions. Increasing polymer concentration in the solid dispersions resulted in greater dissolution enhancement. At a drug/polymer weight ratio of 1:9, complete drug release was achieved after 60 min without any evidence of recrystallization for up to 72 h. After achieving a drug concentration of 71.61 ± 0.32 μg/mL after 24 h from the 3:7 solid dispersions, CX recrystallized thereafter reaching a concentration of 56.09 ± 0.19 and 53.37 ± 0.28 μg/mL after 48 and 72 h, respectively. Solid dispersions at a drug/polymer weight ratio of 1:1 achieved a drug concentration of 13.24 ± 0.21 μg/mL after 48 h; recrystallization of CX occurred after 72 h (10.96 ± 0.16 μg/mL). Conversely, solid dispersions with a drug/polymer weight ratio of 7:3 achieved a steady but reduced CX concentration compared to other drug/polymer ratios (between 4 and 5 μg/mL) after 24 h.

It has been reported in the literature that polymers having pH dependent solubility may enhance the dissolution properties of poorly soluble drugs from solid dispersions at pH in which these polymers are soluble. Eudragit EPO, a cationic polymer, is soluble at pH less than 5 and permeable at higher pH values.[7] Melt extrudates prepared using Eudragit EPO showed significant enhancement in indomethacin solubility compared to physically mixed samples in simulated gastric fluid (SGF) pH 1.5. This enhancement in drug solubility in SGF was greater from the solid dispersion at higher polymer concentrations. Conversely, in simulated intestinal fluid (SIF) pH 6.8, the improvement of drug solubility was significantly lower compared to SGF and the increase in solubility was inversely related to polymer concentration due to the poor solubility of EPO at pH 6.8. In addition, EPO has also been shown to provide significant improvement in the dissolution performance of CX.[30] Moreover, Eudragit L100-55 polymer, which is soluble at pH ≥ 5.5, was used to prepare itraconazole solid dispersions.[38] The drug dissolution from solid dispersions generated significantly greater supersaturated drug levels in pH 6.8 at higher polymer to drug ratio than lower ratios. Furthermore, HPMCAS (grade MF), soluble at pH ≥ 6.0, generated greater supersaturated levels of felodipine at pH 6.8 and maintained these concentrations for longer times compared to PVP and HPMC.[21] The supersaturated levels generated by the polymers increased with increasing polymer concentration in the solid dispersions. The role of Eudragit 4155F in enhancing drug solubility was further confirmed when nearly comparable dissolution profiles were generated from the physically mixed samples containing crystalline or amorphous CX at a drug/polymer weight ratio of (1:9) achieving an equilibrium concentration of 64.25 ± 1.04 and 64.91 ± 0.35 (μg/mL) (p = 0.3563), respectively, after 72 h. These results confirmed that drug release properties of CX from Eudragit 4155F solid molecular dispersions were highly dependent on the polymer and the intimate mixing between the drug and the polymer rather than the solid-state properties of CX.

To determine if polymer dissolution rate influenced drug release properties we examined the dissolution performance of extrudates at an elevated pH using a dissolution medium with a pH of 9.4. A significant enhancement in CX drug release from the solid dispersions was achieved in comparison to dissolution at pH 7.4 (Figures 4 and 5). Solid dispersions containing drug/polymer weight ratio of 1:9 reached complete drug release in shorter time periods (within 30 min) and remained at this level for 72 h. A drug/polymer weight ratio of 3:7 showed complete drug release after 30 min. This was maintained for 5 h and then recrystallization occurred and a concentration of 83.63 ± 0.14 μg/mL was observed after 6 h which stabilized at 72 h (80.83 ± 0.79 μg/mL). A drug/polymer weight ratio at 1:1 showed a maximum concentration of 34.95 ± 0.31 μg/mL after 2 h and then recrystallized rapidly reaching a concentration of 13.18 ± 0.03 μg/mL after 6 h then achieving an equilibrium concentration of 9.30 ± 0.07 μg/mL after 72 h. A drug/polymer ratio of 7:3 showed a peak concentration after 2 h of 9.58 ± 0.19 μg/mL and then decreased slightly and stabilized at a concentration 4.83 ± 0.16 μg/mL after 72 h. The significant increase in the drug dissolution properties from the solid dispersions may be attributed to the higher dissolution properties of Eudragit 4155F at pH 9.4 than at pH 7.4, given that the equilibrium solubility of crystalline CX at pH 9.4 was not significantly different than at pH 7.4 (1.56 ± 0.12 μg/mL) (p = 0.7978). Eudragit 4155F is an anionic polymer which has a pH dependent solubility, and it is only soluble at pH > 7.0, so increasing the pH of test fluid to 9.4 resulted in more ionization of the free carboxylic acid groups of Eudragit 4155F and hence faster drug release properties from the solid dispersions. The drug release rate of 5-aminosalicylic acid from

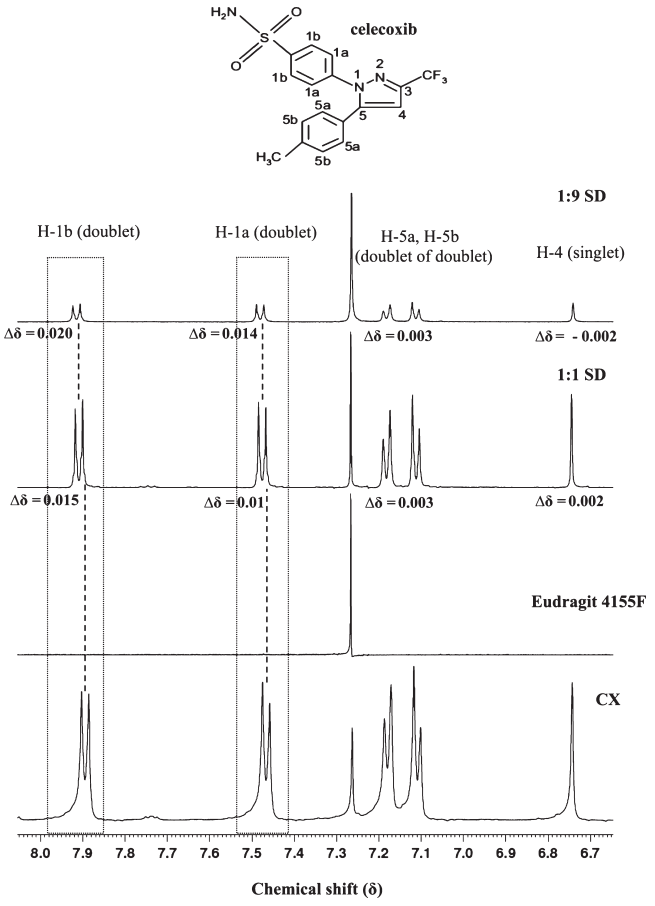

Figure 6. Solution ^{1}H NMR spectra of CX, Eudragit 4155F and CX/Eudragit 4155F solid dispersions (SD). The chemical structure of celecoxib (CX) with proton assignments is shown at the top of the figure. $\Delta\delta$ represents the change in the chemical shift for the H atoms of CX in solid dispersions samples ($\Delta\delta = \delta$SD $- \delta$CX).

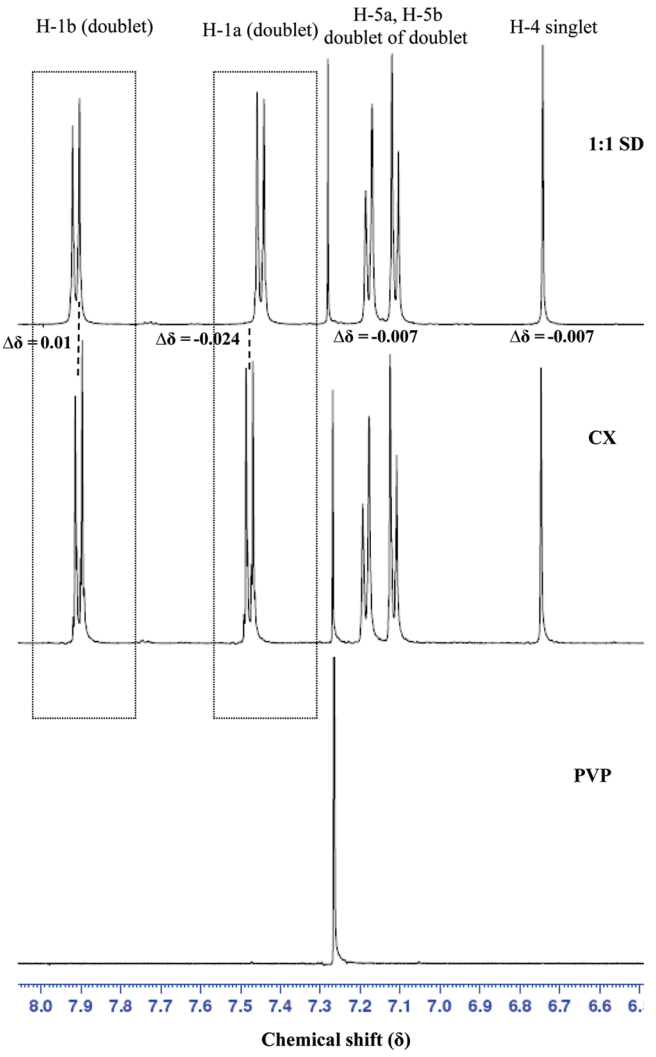

Figure 7. Solution ^{1}H NMR spectra of CX, PVP and CX/PVP solid dispersions (SD). $\Delta\delta$ represents the change in the chemical shift for the H atoms of CX in solid dispersions samples ($\Delta\delta = \delta$SD $- \delta$CX).

Eudragit S100, an anionic polymer which is soluble at pH > 7.0, increased significantly when the pH increased from 6.8 to 7.4 as a result of increasing ionization of its free carboxylic acid.[24]

Supersaturated solutions generated by dissolution of the amorphous solid dispersions can arise from stabilizing effects of polymers[14,15] and/or by the increase in the equilibrium solubility of the crystalline drug due to complexation in solution with the polymer and hence a reduced extent of supersaturation and a lowered thermodynamic driving force for crystallization.[16,21] Based on the results of dissolution of the amorphous solid dispersions at 1:9 and 3:7 ratios, which showed significantly greater drug concentrations compared to the theoretical solubility of amorphous CX, it may be suggested that the later mechanism may be more applicable in the CX/Eudragit 4155F system. The dissolution enhancement in the presence of 4155F may be related to an increase in the intrinsic dissolution rate. This may be attributed to the formation of a soluble complex between drug and polymer during dissolution.[39] In previous studies, felodipine solubility has been enhanced significantly from solid dispersions using hydrophilic polymer concentrations exceeding 75% w/w due to the formation of soluble drug−polymer complexes.[40] Therefore, it is not unreasonable to assume that a similar mechanism of dissolution enhancement is operating within the CX/4155F solid dispersions. The possibility of formation of a soluble complex was further investigated using solution ^{1}H NMR.

Solution ^{1}H NMR. ^{1}H NMR spectroscopic studies were performed in order to investigate the presence of drug−polymer interactions that may occur in solution and to try to correlate this data with the results obtained from dissolution experiments of solid dispersions. Solution ^{1}H NMR spectra were generated for CX, polymers and solid dispersions in order to investigate whether the electron density around the H atoms of CX varied as a result of interactions between CX and the polymers. If interactions occur, it should be reflected in chemical shift variations, since the electron density at the interacting atoms will be changed.[13]

The chemical shifts (δ) of the aromatic protons of CX containing the sulfonamide group $-SO_2NH_2$ (H-1a and H-1b) have been shifted downfield to higher values (deshielding) in solutions resulted from dissolution of Eudragit 4155F solid dispersions particularly at higher polymer concentrations compared to the corresponding protons in pure CX (Figure 6). These deshielding effects on the aromatic protons containing the sulfonamide group suggest a change in electron density as a result of interaction with

Eudragit 4155F. The downfield shifts of (H-1a) and (H-1b) protons of CX at higher polymer concentrations correlate well with the solubilizing effect of Eudragit 4155F on CX at increasing polymer concentration. These findings strongly suggest the interaction (complex formation) between CX and Eudragit 4155F during the dissolution process that resulted in significant enhancement in drug solubility.

It has been previously reported that hydrophilic carriers can interact with drug molecules in solution forming weakly soluble complexes mainly by electrostatic forces (ion−ion, ion−dipole, and dipole−dipole bonds) and occasionally by other types of forces like van der Waals forces and hydrogen bonding.[28,29] Carriers used to prepare solid dispersions may increase the solubility of drugs by forming weakly soluble complexes similar to those reported for cyclodextrins.[27] Sinha et al.[41,42] confirmed complex formation between CX and β-cyclodextrin using solution ^{1}H NMR based on downfield shifts (deshielding) for CX (H-1a and H-1b) protons resulting in significant enhancement in the solubility of CX. Additionally, complexation between β-cyclodextrin (β-CD) and fluconazole was confirmed by solution ^{1}H NMR which showed deshielding of the aromatic protons of fluconazole (*m*-difluorophenyl ring). The proximity of protons to an electronegative atom (e.g., oxygen) withdraws electrons from the aromatic ring, resulting in deshielding and hence movement to a higher position, i.e., increased ppm.[43] Similar trends were observed in CX/Eudragit 4155F solid dispersions during dissolution as a result of the effect of the electronegative carbonyl groups of Eudragit 4155F that may withdraw electrons from the aromatic protons of CX resulting in deshielding and the formation of a soluble complex. Solution ^{1}H NMR suggested complex formation between PVP and felodipine at higher polymer concentrations.[40] Deshielding of felodipine amino protons occurred in dispersions containing high PVP concentrations (>75% w/w) as a result of hydrogen bonding interactions with the carbonyl group of PVP. Only a significant increase in the drug solubility was achieved at polymer concentrations exceeding 75% w/w. These results suggest that the intensity of interaction significantly affects dissolution enhancement. Within this study, the most interesting differences between the ^{1}H NMR spectra of CX/PVP solid dispersions and CX were the deshielding and shielding effects on protons (H-1a) and (H-1b) of the aromatic ring containing the sulfonamide group (Figure 7). These effects suggest changes in the electron density due to interaction with PVP in solution. The aromatic protons (H-1b) were shifted downfield to higher chemical shifts (deshielding) particularly at higher polymer concentrations. Conversely, (H-1a) aromatic protons were shifted upfield to lower chemical shifts (shielding). These different effects suggest that CX interacts in a different way with PVP in comparison to Eudragit 4155F in solution which goes some way toward explaining the different polymer effects, particularly in terms of inhibition of CX recrystallization and dissolution of amorphous drug. Certain types of molecular association are needed to achieve crystallization, so disruption of the molecular interactions between drug molecules may result in inhibition of crystal lattice formation.[44] The interactions between CX and PVP may prevent CX molecules in solution from ordering themselves to form the required intermolecular forces needed to form the crystal lattice and hence inhibit recrystallization.

CONCLUSION

In this study, it has been shown that supersaturated drug concentrations generated from the dissolution of amorphous solid dispersions were due to different polymeric effects. The solubilizing effect of Eudragit 4155F was the dominant mechanism for the release of CX from the solid dispersions. This solubilizing polymeric effect was highly dependent on the polymer concentration and the pH of the test fluid rather than the solid-state properties of the drug. Additionally, this study highlighted the importance of the intimate drug/polymer mixing achieved by HME in increasing the supersaturated drug concentrations compared to the physically mixed samples. The high efficiency of Eudragit 4155F to enhance CX solubility may be clinically important particularly in colonic medium, in which there is low motility and fluid content. Conversely no such solubilizing effects have been observed when using PVP. However, the supersaturated levels generated by amorphous CX were stabilized efficiently by PVP. This stabilizing polymeric effect may be attributed to certain specific interactions formed between CX and PVP in solution that might prevent the molecular association of CX required to form a stable crystal lattice during recrystallization.

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REFERENCES

(1) Chiou, W. L.; Riegelman, S. Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.* **1971**, *60*, 1281–1302.

(2) Hancock, B. C.; Zografi, G. Characteristics and significance of the amorphous state in pharmaceutical systems. *J. Pharm. Sci.* **1997**, *86*, 1–12.

(3) Serajuddin, A. M. Solid dispersion of poorly water-soluble drugs: early promises subsequent problems, and recent breakthroughs. *J. Pharm. Sci.* **1999**, *88* (10), 1058–1066.

(4) Leuner, C.; Dressman, J. Improving drug solubility for oral delivery using solid dispersions. *Eur. J. Pharm. Biopharm.* **2000**, *50*, 47–60.

(5) Forster, A.; Hempenstall, J.; Rades, T. Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers. *J. Pharm. Pharmacol.* **2001**, *53*, 303–315.

(6) Breitenbach, J.; Mägerlein, M. Melt extruded molecular dispersions. In *Pharmaceutical extrusion technology. Drugs and the pharmaceutical sciences*, 1st ed.; Ghebre-Sellassie, I., Martin, C., Eds.; Marcel Dekker Inc.: New York, 2003.

(7) Chokshi, R. J.; Shah, N. H.; Sandhu, H. K.; Malick, A. W.; Zia, H. Stabilization of low glass transition temperature indomethacin formulations: impact of polymer-type and its concentration. *J. Pharm. Sci.* **2008**, *97* (6), 2286–2298.

(8) Breitenbach, J. Melt extrusion: from process to drug delivery technology. *Eur. J. Pharm. Biopharm.* **2002**, *54*, 107–117.

(9) Crowley, M. M.; Zhang, F.; Repka, M. A.; Thumma, S.; Upadhye, S. B.; Battu, S. K. Pharmaceutical applications of hot-melt extrusion: Part I. *Drug Dev. Ind. Pharm.* **2007**, *33*, 909–926.

(10) Taylor, L. S.; Zografi, G. Spectroscopic characterization of interactions between PVP and indomethacin in amorphous molecular dispersions. *Pharm. Res.* **1997**, *14*, 1691–1698.

(11) Huang, J.; Wigent, R. J.; Schwartz, J. B. Drug−polymer interaction and its significance on the physical stability of nifedipine amorphous dispersion in microparticles of an ammonio methacrylate

copolymer and ethylcellulose binary blend. *J. Pharm. Sci.* **2008**, *97* (1), 251–262.

(12) Andrews, G. P.; Abu-Diak, O.; Jones, D. S. Physicochemical characterization of hot-melt extruded bicalutamide-polyvinylpyrrolidone solid dispersions. *J. Pharm. Sci.* **2010**, *99* (3), 1322–1335.

(13) Van den Mooter, G.; Wuyts, M.; Blaton, N.; Busson, R.; Grobet, P.; Augustijns, P.; Kinget, R. Physical stabilization of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. *Eur. J. Pharm. Sci.* **2001**, *12*, 261–269.

(14) Tanno, F.; Nishiyama, Y.; Kokubo, H.; Obara, S. Evaluation of hypromellose acetate succinate (HPMCAS) as a carrier in solid dispersions. *Drug Dev. Ind. Pharm.* **2004**, *30*, 9–17.

(15) Gupta, P.; Kakumanu, K. V.; Bansal, A. K. Stability and solubility of celecoxib−PVP amorphous dispersions: a molecular perspective. *Pharm. Res.* **2004**, *21* (10), 1762–1769.

(16) Loftsson, T.; Fridriksdóttir, F.; Gudmundsdóttir, T. K. The effect of water-soluble polymers on aqueous solubility of drugs. *Int. J. Pharm.* **1996**, *127*, 293–296.

(17) Usui, F.; Maeda, K.; Kusai, A.; Nishimura, K.; Yamamoto, K. Inhibitory effects of water-soluble polymers on precipitation of RS-8359. *Int. J. Pharm.* **1997**, *154*, 59–66.

(18) Six, K.; Verreck, G.; Peeters, J.; Brewster, M.; Van den Mooter, G. Increased physical stability and improved dissolution properties of itraconazole, a class II drug, by solid dispersions that combine fast- and slow-dissolving polymers. *J. Pharm. Sci.* **2004**, *93* (1), 124–131.

(19) Miller, D.; DiNunzio, J. C.; Yang, W.; McGinity, J. W.; Williams, R. O., III. Targeted intestinal delivery of supersaturated itraconazole for improved oral absorption. *Pharm. Res.* **2008**, *25*, 1450–1459.

(20) Nollenberger, K.; Gryczke, A.; Meier, C.; Dressmn, J.; Schmidt, M. U.; Brühne, S. Pair distribution function X-ray analysis explains dissolution characteristics of felodipine melt extrusion products. *J. Pharm. Sci.* **2009**, *98* (4), 1476–86.

(21) Konno, H.; Handa, T.; Alonzo, D. E.; Taylor, L. S. Effect of polymer type on the dissolution profile of amorphous solid dispersions containing felodipine. *Eur. J. Pharm. Biopharm.* **2008**, *70*, 493–499.

(22) Takaya, T.; Niwa, K.; Muraoka, M.; Ogita, I.; Nagai, N.; Yano, R.; Kimura, G.; Yoshikawa, Y.; Yoshikawa, H.; Takada, K. Importance of dissolution process on systemic availability of drugs delivered by colon delivery system. *J. Controlled Release* **1998**, *50*, 111–122.

(23) Lu, B.; Zhang, Z. Novel colon-specific microspheres with highly dispersed hydroxycamptothecin cores: their preparation, release behavior, and therapeutic efficiency against colonic cancer. *J. Pharm. Sci.* **2006**, *95* (12), 2619–2630.

(24) Bruce, L. D.; Shah, N. H.; Malick, A. W.; Infeld, M. H.; McGinity, J. W. 2005. Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid. *Eur. J. Pharm. Biopharm.* **2005**, *59*, 85–97.

(25) Zhu, Y.; Mehta, K. A.; McGinity, J. W. Influence of plasticizer level on the drug release from sustained release film coated and hot-melt extruded dosage forms. *Pharm. Dev. Technol.* **2006**, *11*, 285–294.

(26) Andrews, G. P.; Abu-Diak, O.; Kusmanto, F.; Hornsby, P.; Hui, Z.; Jones, D. S. Physicochemical characterization and drug-release properties of celecoxib hot-melt extruded glass solutions. *J. Pharm. Pharmacol.* **2010**, *62* (11), 1580–1590.

(27) Craig, D. Q. M. The mechanisms of drug release from solid dispersions in water-soluble polymers. *Int. J. Pharm.* **2002**, *231*, 131–144.

(28) Cirri, M.; Mura, P.; Rabasco, A. M.; Ginés, M.; Moyano, J. R.; Gonzalez-Rodrıguez, M. L. Characterization of ibuproxam binary and ternary dispersions with hydrophilic carriers. *Drug Dev. Ind. Pharm.* **2004**, *30* (1), 65–74.

(29) Ahuja, N.; Katare, O. P.; Singh, B. Studies on dissolution enhancement and mathematical modelling of drug release of a poorly water-soluble drug using water-soluble carriers. *Eur. J. Pharm. Biopharm.* **2007**, *65*, 26–38.

(30) Albers, J.; Alles, R.; Matthée, K.; Knop, K.; Nahrup, J. S.; Kleinebudde, P. Mechanism of drug release from polymethacrylate-based extrudates and milled strands prepared by hot-melt extrusion. *Eur. J. Pharm. Biopharm.* **2008**, *71* (2), 387–394.

(31) Goddeeris, C.; Willems, T.; Houthoofd, K.; Martens, J. A.; Van Den Mooter, G. Dissolution enhancement of the anti-HIV drug UC 781 by formulation in a ternary solid dispersion with TPGS 1000 and Eudragit® E100. *Eur. J. Pharm. Biopharm.* **2008**, *70*, 861–868.

(32) Hancock, B. C.; Parks, M. What is the true solubility advantage for amorphous pharmaceuticals? *Pharm. Res.* **2000**, *17*, 397–404.

(33) Parks, G. S.; Huffman, H. M.; Cattor, F. R. Studies on glass. II: the transition between the glassy and liquid states in the case of glucose. *J. Phys. Chem.* **1928**, *32*, 1366–1379.

(34) Parks, G. S.; Snyder, L. J.; Cattoir, F. R. Studies on glass. XI: some thermodynamic relations of glassy and alpha-crystalline glucose. *J. Chem. Phys.* **1934**, *2*, 595–598.

(35) Marsac, P.; Konno, H.; Taylor, L. S. A comparison of the physical stability of amorphous felodipine and nifedipine systems. *Pharm. Res.* **2006**, *10*, 2306–2316.

(36) Janssens, S.; Van den Mooter, G. Review: physical chemistry of solid dispersions. *J. Pharm. Pharmacol.* **2009**, *61*, 1571–1586.

(37) Lu, Q.; Zografi, G. Phase behavior of binary and ternary amorphous mixtures containing indomethacin, citric acid, and PVP. *Pharm. Res.* **1998**, *15*, 1202–1206.

(38) Overhoff, K. A.; Moreno, A.; Miller, D. A.; Johnston, K. P.; Williams, R. O., III. Solid dispersions of itraconazole and enteric polymers made by ultra-rapid freezing. *Int. J. Pharm.* **2007**, *336*, 122–132.

(39) Sethia, S.; Squillante, E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. *Int. J. Pharm.* **2004**, *272*, 1–10.

(40) Karavas, E.; Ktistis, G.; Xenakis, A.; Georgarakis, E. Effect of hydrogen bonding interactions on the release mechanism of felodipine from nanodispersions with polyvinylpyrrolidone. *Eur. J. Pharm. Biopharm.* **2006**, *63*, 103–114.

(41) Sinha, V. R.; Anitha, R.; Ghosh, S.; Nanda, A.; Kumaria, R. Complexation of Celecoxib with β-Cyclodextrin: Characterization of the interaction in solution and in solid state. *J. Pharm. Sci.* **2005**, *94* (3), 676–687.

(42) Sinha, V. R.; Anitha, R.; Ghosh, S.; Kumaria, A. R.; Bhinge, J. R. Physicochemical characterization and *in vitro* dissolution behaviour of celecoxib-cyclodextrin inclusion complexes. *Acta Pharm.* **2007**, *57*, 47–60.

(43) Upadhyay, S. K.; Kumar, G. NMR and molecular modelling studies on the interaction of fluconazole with β-cyclodextrin. *Chem. Cent. J.* **2009**, *3*, 9http://journal.chemistrycentral.com/content/3/1/9.

(44) Tang, X. C.; Pikal, M. J.; Taylor, L. S. A spectroscopic investigation of hydrogen bond patterns in crystalline and amorphous phases in dihydropyridine calcium channel blockers. *Pharm. Res.* **2002**, *19*, 477–483.