Physicochemical characterization and drug-release properties of celecoxib hot-melt extruded glass solutions

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Abstract

The interest in hot-melt extrusion (HME) as a drug delivery technology for the production of glass solutions is growing rapidly. HME glass solutions have a tendency to recrystallize during storage and also typically have a very dense structure, restricting the ingress of dissolution fluid and retarding drug release. In this study, we have used HME to manufacture glass solutions containing celecoxib (CX) and polyvinylpyrrolidone (PVP) and have assessed the use of supercritical carbon dioxide ($scCO_2$) as a pore-forming agent to enhance drug release. Differential scanning calorimetry confirmed the formation of glass solutions following extrusion. All extrudates exhibited a single glass transition temperature (T_g), positioned between the T_g values of CX and PVP. The instability of glass solutions is a significant problem during storage. Stabilization may be improved through the appropriate choice of excipient to facilitate drug–polymer interactions. The Gordon–Taylor equation showed that the T_g values of all extrudates expected on ideal mixing were lower than those observed experimentally. This may be indicative of drug–polymer interactions that decrease free volume and elevate the T_g. Molecular interactions between CX and PVP were further confirmed using Fourier transform infrared and Raman spectroscopy. Storage stability of the extrudates was shown to be dependent on drug loading. Samples containing a higher CX loading were less stable, which we ascribed to decreased T_g and hence increased mobility within the drug–polymer matrix. The solubility of CX was improved through the formulation of extruded glass solutions, but release rate was relatively slow. Exposure of extrudates to $scCO_2$ had no effect on the solid-state properties of CX but did produce a highly porous structure. The drug-release rate from extrudates after $scCO_2$ exposure was significantly higher.

Keywords celecoxib; glass solutions; melt extrusion; solid dispersions

Introduction

Hot-melt extrusion (HME) is a non-ambient process that converts a drug compound and excipients into a product of uniform shape and density by forcing them through an extrusion barrel and subsequently a die at defined temperature, screw speed and pressure.[1] This technology offers many advantages over traditional solid-dosage form manufacturing methods. In particular, more than one unit operation (e.g. mixing, melting and homogenizing) may be performed in a single continuous step, providing a robust platform for scale up. Furthermore, the high throughput, low material loss and the ability to use powders with a range of particle sizes, compressibility and/or compaction properties make it suitable for a large range of drugs. In relation to drug delivery, HME has been shown to be extremely versatile and has been used to produce drug-delivery platforms with immediate-, sustained- and controlled-release properties.[2] More specifically, HME has been shown to be a viable technology for the production of oral solid-dosage forms. In this respect, several research groups have demonstrated the viability of HME for the production of orally administered tablets.[3]

Over the last decade the number of poorly soluble drugs has increased significantly. Currently it is estimated that >50% of all new chemical entities have little or no water solubility, which represents a significant challenge for oral administration. The low bioavailability of such compounds may be readily improved if dissolution within gastrointestinal fluids can be enhanced and maintained long enough for transport across the absorptive

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gastrointestinal membrane. Addressing the challenge of poor aqueous solubility is therefore of significant academic and industrial relevance. HME is an attractive technology for the production of glass solutions that offer improved aqueous solubility for Biopharmaceutical Classifiction System (BCS) class II drugs. However, HME tablets typically have a dense structure with low porosity. This may hinder drug release from the polymeric matrix as a result of the slow penetration of gastrointestinal fluids through the matrix. Delaying the release of a drug could potentially lower bioavailability, particularly if the compound has a narrow absorption window within the gastrointestinal tract.

Celecoxib (CX) is a weakly acidic, hydrophobic drug with low aqueous solubility. Consequently, CX has highly variable absorption after oral administration. To achieve maximum therapeutic benefit, rapid onset of action is necessary to provide immediate relief for the treatment of acute pain. It is therefore not only necessary to enhance the aqueous solubility of CX but also to obtain an enhanced dissolution rate to achieve fast onset of action, minimize the variability in absorption and improve the overall oral bioavailability.[4]

Formulation of CX into solid dosage forms using traditional processes is often difficult due to the physical properties of the drug powder. CX exists as acicular crystals that are extremely cohesive. It has a low bulk density, poor compressibility and uneven flow properties. Furthermore, the particle size of CX influences the content uniformity, dissolution and bioavailability of its pharmaceutical products. Consequently, CX represents a highly appropriate model drug for HME processing since, using this technology, we may avoid the problematic powder-handling properties of the drug and may also enhance drug aqueous solubility through the formation of glass solutions. Whilst HME may provide a suitable means by which we may enhance drug dissolution, the high density of the formed tablet may restrict the associated benefits of glass solution formation. Currently this effect has been largely overlooked within the scientific literature. In this study we have addressed this deficit by examining the potential of HME as a processing platform to produce HME tablets containing solid molecular dispersions of CX with a hydrophilic polymer. We have also studied the effect of both milling and exposure to scCO₂ as a means of increasing surface area to improve the drug dissolution rate.

Materials and Methods

Materials

CX was a kind gift from Hikma Pharmaceuticals (Amman, Jordan), polyvinylpyrrolidone (PVP) K25 and Triton® X-100 were purchased from Sigma-Aldrich Chemie GmbH (Poole, Dorset, UK). All other chemicals used were purchased from BDH Laboratory supplies (Poole, Dorset, UK) and were of Analar grade or equivalent quality.

Methods
Preparation of CX-PVP melt extrudates
CX was mixed with PVP at CX : PVP mass ratios of 3 : 7, 1 : 1 and 7 : 3 using a mortar and pestle for 2 min. The physical mixtures (10 g) were extruded using a co-rotating twin-screw extruder (Minilab, Thermo Electron Corporation, Stone, Staffordshire, UK) at a screw speed of 100 rpm and a temperature of 150°C for the 1 : 1 and 7 : 3 ratios. A temperature of 170°C was used for the 3 : 7 ratio. The residence time of the formulations in the extruder was <2 min. The cylindrical melt extrudates, which were transparent in appearance, were milled using a mortar and pestle, and passed through a 355 μm sieve. Melt extrudates, at a CX : PVP ratio of 3 : 7, were also cut into tablets, each having a mass equivalent to 50 mg CX (167 ± 2 mg), that were used in subsequent scCO₂ studies. The extrudates were 2.86 ± 0.06 mm in diameter. All samples were stored in a dessicator containing silica gel at 20°C. A suitable quantity of the physical mixture from each drug : polymer mass ratio was kept for analysis to compare to the corresponding extruded formulations.

Exposure of melt extrudates to scCO₂
CX-PVP HME tablets at a CX : PVP ratio of 3 : 7 were placed in a high-pressure vessel consisting of a CO₂ cylinder, a Thar Technologies P50 high pressure pump and a 250 ml high-pressure vessel. Melt extruded tablets were exposed to CO₂ at a pressure of 100 bar and a temperature of 40°C (above its critical temperature and pressure) to generate scCO₂. After 24 h, the chamber was depressurized and the CO₂ evacuated over a period of 1 min. Samples were either kept as tablets (167 ± 2 mg) or milled and sieved through a 355 μm sieve. All samples were stored in a desiccator over silica gel at 20°C.

Preparation of an amorphous CX–PVP physical mixture
Amorphous CX was prepared by heating CX up to 170°C for 2 min using a stainless steel beaker, then rapidly quench cooling the molten sample in an ice bath. The generation of amorphous CX was confirmed using differential scanning calorimetry (DSC). The prepared amorphous CX was subsequently mixed with PVP at a drug : polymer mass ratio of 3 : 7 using a mortar and pestle.

Thermogravimetric analysis
The thermal stability of CX and PVP was studied using a TA instruments Q500 TGA (Leatherhead, UK). Ramp tests were performed at a scan speed of 10°C/min over a range from 20 to 500°C. Isothermal tests were conducted by heating the samples to 170°C and holding at this temperature for 60 min. Nitrogen was used as the purging gas during all thermogravimetric analysis (TGA) experiments.

Differential scanning calorimetry
DSC analyses were conducted using a TA instruments Q100 DSC (Leatherhead, UK) equipped with a refrigerated cooling system. All data analyses were performed using Universal Analysis 2000 software. In brief, samples of between 5.0 and 10.0 mg were accurately weighed and placed in crimped aluminium 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. For glass transition temperature (T_g) determination, the samples were subjected to a heat–cool–heat cycle and the T_g calculated

as the midpoint of the step transition in the plot of heat flow versus temperature in the second heat cycle.

Gordon–Taylor calculations

The T_g values of CX–PVP binary systems were estimated using the Gordon–Taylor equation shown below. These values were subsequently compared to the T_g values of samples observed experimentally.

$$T_{gmix} = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \qquad (1)$$

$$K \approx \frac{T_{g1} \rho_1}{T_{g2} \rho_2} \qquad (2)$$

Tg_1 and Tg_2 are the glass transition temperatures, and w_1 and w_2 are the weight fractions of the drug and polymer. K may be estimated from the density (ρ) and Tg of the amorphous form of CX and PVP. The true densities (ρ) of amorphous CX and PVP were determined to be 1.35 and 1.18 g/cm^3, respectively, measured using an AccPyc 1330 helium pycnometer (Micromeritics®, Norcross, USA).

Powder X-ray diffractometry

Powder X-ray diffractometry (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 Kα1 radiation was used as an X-ray source. Soller slits (0.04 rad) were used for the incident and diffracted beam paths. The angular range (3–60 2θ) was scanned in continuous mode using 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.

Scanning electron microscopy

Scanning electron microscopy (SEM) was used to study the surface morphology of the extrudates (pre and post scCO$_2$ exposure). Samples were mounted onto aluminium discs using double-sided adhesive copper mounting tape and placed in a dry atmosphere under vacuum overnight, prior to coating and analysis. Samples were subsequently coated with a thin film of gold (15 nm) using an Agar® Auto Gold Sputter Coater. SEM was performed using a JEOL 6500F field emission microscope operating at an accelerating voltage of either 2 or 5 kV with a 4 µA beam current emission. Images were captured using Jeol® software.

Fourier transform infrared spectroscopy

Fourier transform infrared (FTIR) analyses were performed using a Fourier transform infrared spectrophotometer model 4100 (FT/IR-4100) (Jasco, Japan) and Jasco Spectra Manager Version 2 software. A small mass of each sample was mixed with dry potassium bromide using a mortar and pestle and compressed to prepare a disk.

Raman spectroscopy

Raman spectra were obtained using an Avalon Raman station R3 Model AVRS003A spectrometer from Avalon Instruments Ltd (Belfast, UK). Grams/AI version 7.02 spectral data processing software from Thermo Galactic™, a product of Thermo Fischer Scientific, was used to process spectra.

In-vitro drug release studies

In-vitro drug dissolution profiles for CX, physical mixtures and melt extrudates (pre and post scCO$_2$ exposure), either as formed tablets or milled samples, were examined using a paddle method (USP 30, 2007). Samples equivalent to 50 mg of CX were added to the dissolution medium (500 ml) consisting of simulated gastric fluid, without pepsin and containing 0.1% (w/v) Triton®-X100 at a temperature of 37 ± 0.1°C. The solution was stirred using a rotating paddle at 100 rpm. Five-millilitre aliquots were withdrawn from each vessel at predetermined time intervals (5, 10, 15, 30, 45, 60, 90, 120, 180, 240 and 300 min) and filtered over a cellulose acetate filter (0.45 µm, Nalgene Labware, Rochester, USA). The concentration of CX in each sampled aliquot was determined using a Cary 50 (Varian Ltd, Oxford, UK) UV-VIS spectrophotometer at 250 nm and a standard calibration curve that was linear over the concentration range (2.5–20 µg/ml). Drug dissolution analyses were conducted at least in triplicate.

Stability study

Stability studies were conducted at 40°C and 75% relative humidity (RH) during a 3-month period. Samples of HME tablets (pre and post scCO$_2$ exposure), milled melt extrudates and a physical mixture of amorphous CX with PVP were placed in open glass vials and stored in open pans at 40°C inside a dessicator containing a saturated sodium chloride solution. PXRD was used to qualitatively define the presence of crystalline drug content. Drug dissolution studies were also conducted on HME tablets stored for a period of 3 months and compared to the corresponding HME formulations tested immediately after manufacture.

Statistical analysis

A two-tailed one sample t-test was used to compare the experimental T_g values of CX–PVP systems versus the theoretical values calculated using the Gordon–Taylor equation ($\alpha = 0.05$). (The effect of the formulation, process and storage at 40°C, 75% RH on drug dissolution was statistically analysed using a repeated measures one-way ANOVA. Individual differences in drug dissolution between formulations were statistically identified using Fisher's protected least significant difference test. In all cases $P < 0.05$ denoted significance.

Results and Discussion

Solid-dispersion approaches to drug dissolution enhancement typically involve the generation of a glass solution in which the drug is present in a metastable amorphous state possessing a high internal energy and specific volume. This results in a system with a tendency (thermal and/or humidity stress) for recrystallization during storage. It has been previously reported that the stability of high-energy systems is governed

by molecular mobility and drug/polymer miscibility, with factors such as matrix hygroscopicity, viscosity, glass transition temperature and secondary interactions between drug and polymer having a significant influence.[5] Consequently in the formulation and design of glass solutions it becomes extremely important to have analytical methods that allow for screening of these factors and the role they may have on the physicochemical properties of the dispersion. In particular, methods such as DSC, PXRD, drug dissolution, SEM and spectroscopic (FTIR and Raman) techniques are often used for this purpose.

CX is a weakly acidic (pKa = 11.1), poorly soluble non-steroidal anti-inflammatory drug (NSAID), which has a low aqueous solubility and high absorption variability following oral administration.[4] Formulations of CX that offer enhanced solubility and rapid release are highly desirable since they would provide fast relief in the treatment of acute pain. In this study we have investigated the feasibility of HME to produce glass solutions of CX using PVP as a matrix former. Due to the high density of HME products we have additionally examined the effect of milling and the use of scCO₂ on the release properties of the formed extrudates, with the aim of producing a glass solution of CX with a fast-release profile.

Materials used in non-ambient processes require good thermal stability. Even though the residence time within an extruder is relatively short, an understanding of material performance at high temperature is required prior to extrusion. TGA has been used successfully for this purpose to determine volatile degradants. In this study, TGA was used to determine the suitability of CX and PVP for HME. Degradation temperatures for CX and PVP, determined using a TGA ramp test, were shown to occur at 250 and 310°C, respectively. Furthermore, isothermal tests at 170°C showed negligible mass loss over a 60 min period.

Melt extruded products are typically processed at 15–60°C above the glass-transition temperature of a polymer/drug matrix. This ensures that the viscosity of the melt inside the extruder is sufficient to facilitate the production of an acceptable product.[6] DSC was used to confirm the presence of a melting endotherm for CX at 163.2 ± 0.9°C which had an enthalpy of 84.0 ± 4.9 J/g (Figure 1). In order to formulate glass solutions the regular order within the crystal lattice must be destroyed to produce a form of the drug that is molecularly miscible with the polymeric carrier used during the extrusion process. In doing this we are generating a system similar to the amorphous form of the drug with the exception that the polymer and drug exist in a single phase, often stabilized by adhesive interactions between both components. Consequently, the drug within a glass solution may have significant mobility, increased chemical reactivity and may show a high probability towards spontaneous recrystallization. It is extremely important to determine whether the system produced using HME is in the form of a glass solution and, in addition, to determine the stability of this glass over pharmaceutically relevant timescales. A single-phase drug–polymer solution may be identified using a number of techniques, DSC and PXRD being the two most commonly employed. Amorphous CX exhibited T_g at 58.9 ± 0.2°C, a recrystallization exotherm at 131.5 ± 3.1°C and a sharp melting endotherm at 163.0 ± 0.4°C. PVP exhibited T_g at
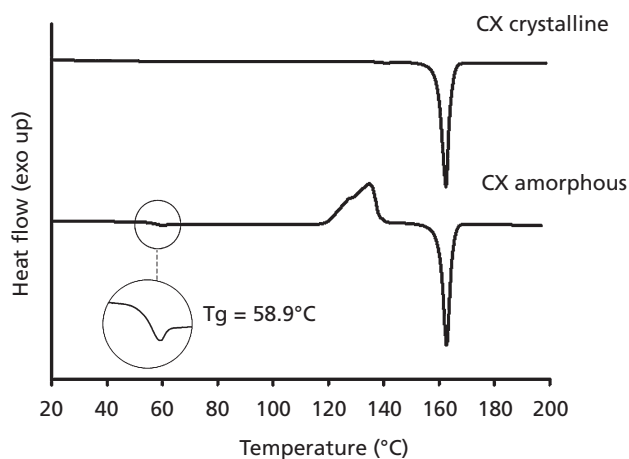

Figure 1 Representative differential scanning calorimetry thermograms of crystalline and amorphous CX. The glass transition of amorphous CX has been expanded for clarity. CX, celecoxib.

154.6 ± 0.7°C. This high T_g meant that PVP could not be extruded at temperatures below 200°C without the use of a suitable plasticizing agent. Whilst conventional liquid plasticizing agents may be used to significantly reduce T_g, it is also extremely important to define the influence of drug inclusion on the polymer glass transition. Previously it has been shown that drug/polymer miscibility facilitates extrusion via a solid-state plasticization effect.[7] In this study, physical mixtures of crystalline CX and PVP were prepared and analysed using DSC. The second heat ramp of DSC thermograms showed a single glass transition between the glass transition temperatures of amorphous CX and PVP. As an example, a physical mixture containing a 3 : 7 drug to polymer ratio exhibited T_g at 120.3 ± 1.2°C. Subsequently, HME trials were conducted to extrude binary mixtures at the lowest possible temperature above the T_g using a screw speed of 100 rpm. At a drug to polymer ratio of 3 : 7, extrusion was possible at a temperature of 170°C whereas at higher drug to polymer ratios (1 : 1 and 7 : 3) extrusion was possible at a temperature of 150°C. In all cases, transparent melt extrudates were produced, providing an initial indication of the formation of a miscible, single-phase system.[8]

The DSC traces of melt extrudates did not exhibit a melting endotherm characteristic of crystalline CX (Figure 2). Instead, a single T_g that was in between the T_g values of both amorphous CX and PVP was observed, further confirming the presence of a single-phase glass solution.[9] In addition, the absence of a recrystallization exotherm for amorphous CX in the extruded samples indicates the ability of PVP to act as an efficient recrystallization inhibitor. This effect is well documented in the scientific literature for a number of different drug types.[10,11] Understanding glass transition temperature shifts is extremely important given that this is indicative of bulk molecular mobility within amorphous drug forms. Consequently, defining positive temperature shifts of the glass transition allows for the identification of polymeric species that may improve storage stability. Samples containing drug and polymer in a ratio of 3 : 7 that had been milled or exposed to scCO₂ displayed no change in T_g (data not shown). This
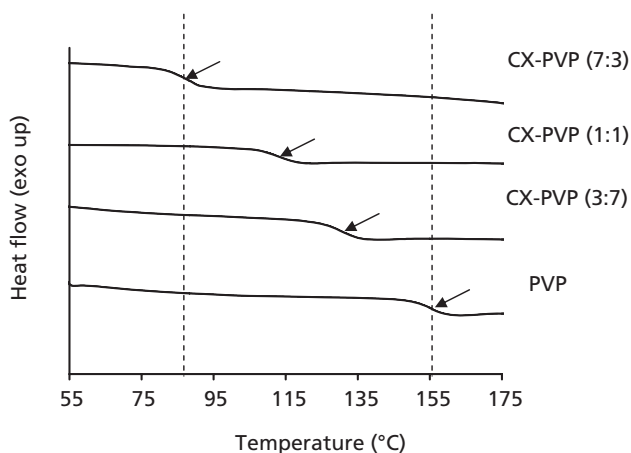
Figure 2 Differential scanning calorimetry thermograms of PVP, CX–PVP hot-melt extrudates. CX, celecoxib; PVP, polyvinylpyrrolidone.

suggests that both post-extrusion processes had negligible effect on the molecular miscibility of the components.

Stabilization of glass solutions is paramount and typically there are three approaches that may be adopted in order to achieve this aim. These include storage of the samples at temperatures significantly below the T_g, thus reducing molecular mobility, increasing drug T_g through the addition of high T_g polymers and cohesive interactions between drug and the polymeric carrier to enhance molecular rigidity.[12] In this study we have used the latter two approaches to engineer stable glass solutions. The T_g values of all extrudates were significantly higher than the value observed for amorphous CX, suggesting that molecular mobility of CX within the extruded systems had been reduced. In such systems the probability of nucleation and crystallization is decreased. Stabilization of an amorphous form of a drug in a polymeric matrix is facilitated by functional group interaction, wherein self-association of active molecules and hence formation of the crystalline form is retarded. Calculation of theoretical T_g values and comparison with experimental values confirmed a positive deviation from ideal behaviour (data not shown). This is indicative of a strong interaction between the two components, most probably secondary in nature, resulting in a decreased free volume, increased network rigidity and a higher T_g.[10] The strong interaction between the two components and subsequent increased network rigidity would assist in stabilizing the high-energy form of CX.

The PXRD patterns for crystalline CX, a typical drug–PVP physical mixture (drug to polymer ratio of 3 : 7) and freshly manufactured HMEs are shown in Figure 3. The most characteristic peaks in the PXRD pattern of crystalline CX are positioned at 2θ angles of 16.0, 19.6, 21.5, 22.3, 23.4, 25.3 and 29.4°. The X-ray pattern of the CX crystalline–PVP physical mixture (3 : 7), which was typical of all physical mixtures, showed the characteristic peaks of crystalline CX with lower intensities, due to dilution of the drug content with PVP. These characteristic peaks were completely absent in all melt extrudates. As expected, those samples that were milled or exposed to scCO$_2$ still retained amorphous character (only scCO$_2$ data shown). This further supported the observations

from DSC experiments, where miscibility between CX and PVP was maintained following both post-processing methods (milling and supercritical fluid treatment).

The T_g is often used as an indicator of amorphous stability and it is commonly suggested that for an amorphous system to remain stable over pharmaceutically relevant timescales it should be stored at a temperature of 50°C below the T_g. In this investigation we stored extrudates for periods of up to 3 months at 40°C and 75% RH. For comparative purposes we also stored a physical mixture of PVP and amorphous CX at a drug to polymer ratio of 3 : 7 w/w. PXRD patterns of the melt extrudates at drug to polymer ratios of 3 : 7 and 1 : 1 w/w retained CX in the amorphous form for 3 months (Figure 4). Melt extrudates containing drug and polymer at a ratio of 7 : 3 were stable for 1 month, but after 2 months very small peaks were observed in the PXRD pattern. The intensity of these peaks increased after 3 months' storage. In comparison, a physical mixture of amorphous CX and PVP recrystallized significantly after 5 days. The results of the storage stability tests confirmed that PVP acts as a solid stabilizer for amorphous CX. The instability of the amorphous CX–PVP physical mixture indicates the importance of HME in forging interaction between the two components. The intimate mixing, facilitated by the high temperatures and shearing forces during extrusion, aids molecular mixing of both components and the generation of a system exhibiting a single T_g of significantly higher value than that observed for amorphous CX. As previously discussed, this antiplasticization effect is dependent on the drug to polymer ratio. Increased drug content within the matrix had a plasticizing effect on the glass solution, significantly decreasing the T_g.[13] Consequently, the formulation containing CX : PVP at a ratio of 7 : 3 had a T_g value of 88.4 ± 0.9°C. Given the close proximity (<50°C) of this T_g to the storage temperature used during stability testing, the reduced stability of this system may be attributed to increased mobility and a greater probability of nucleation and crystal growth. In the other two extruded systems, the T_g values were significantly higher (>50°C) than the storage temperature and thus these two systems showed improved stability.

In order to further understand the interaction between PVP and CX we used both FTIR and Raman spectroscopy to probe molecular interactions. Figure 5 shows the FTIR obtained for a representative hot-melt extrudate, the physical mixture, and PVP and CX (both amorphous and crystalline forms). It has been previously shown that intermolecular interactions within amorphous drug forms have a direct influence on molecular mobility.[14] Moreover, it is well known that secondary interactions, most notably hydrogen bonding, have a considerable influence on structural relaxation, T_g and aqueous solubility. CX possesses several functional groups that may act as proton donors or acceptors and thus facilitate both adhesive and cohesive interactions. The sulfonamide group can act as both a proton donor (NH$_2$) and as a proton acceptor (SO$_2$). In particular, the electron-withdrawing nature of the oxygen atoms on the SO$_2$ results in delocalization of the electrons on the nitrogen atom. This causes positive polarization of the nitrogen atom, facilitating the release of protons. Other proton-accepting groups within CX include the nitrogen atom of the pyrazole group and the fluoride atom of the CF$_3$. In
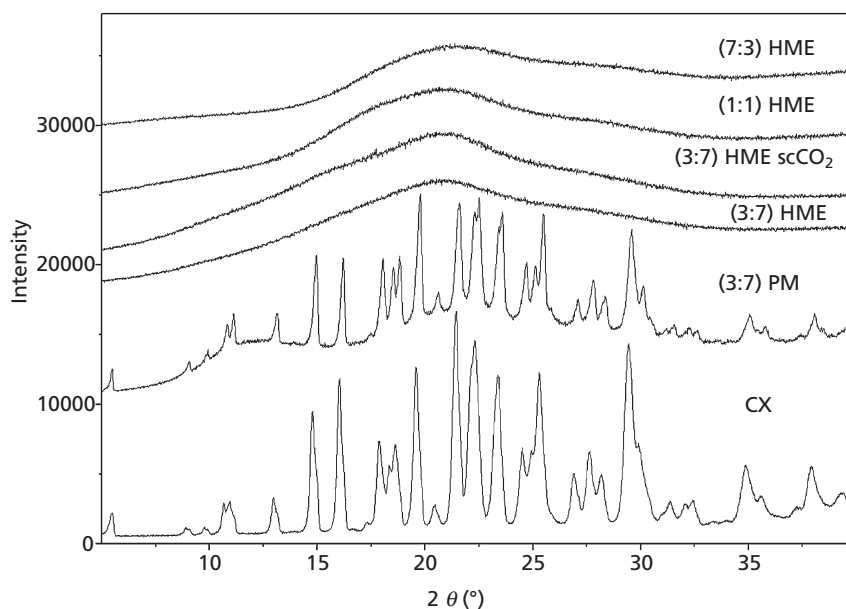
Figure 3 Powder X-ray diffractometry patterns for crystalline CX, a representative physical mixture of crystalline CX and PVP and hot-melt extruded samples immediately following manufacture. HME, hot-melt extruded; scCO$_2$, supercritical carbon dioxide; PM, physical mixture; CX, celecoxib.
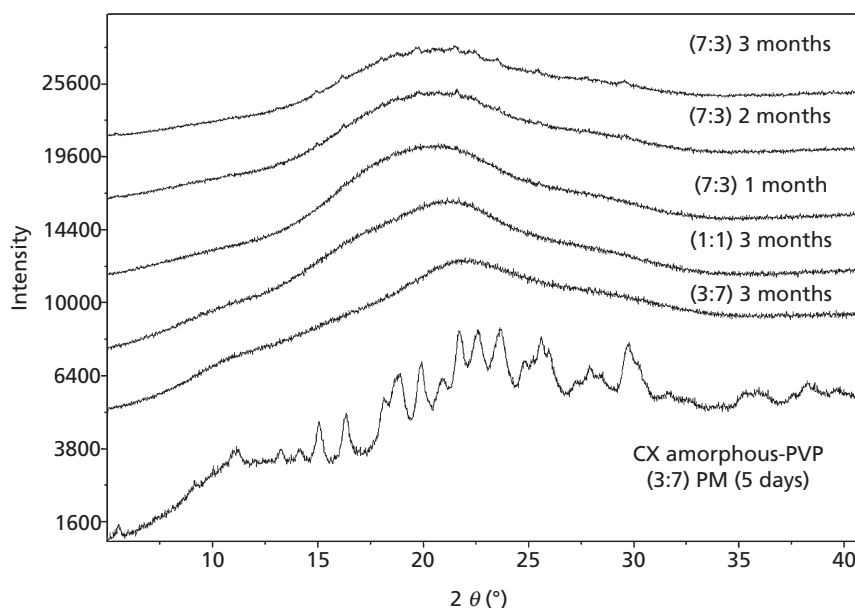

Figure 4 Powder X-ray diffractometry patterns for a physical mixture of amorphous CX and PVP and hot-melt extruded samples stored in open disposable weigh boats at 40°C and 75% RH. CX, celecoxib; PVP, polyvinylpyrrolidone; PM, physical mixture.

comparison, PVP possesses two proton-accepting groups: the oxygen atom of the carbonyl group (C=O) and the nitrogen atom of the pyrrole ring. Due to steric constraints, the C=O group is regarded as the more favourable interaction site. In this study we have shown that there are significant differences between the amorphous and crystalline FTIR and Raman spectra for CX. These differences typically involve the band position for the vibrational modes of the NH, S=O (sulfonyl) and C–F groups. In respect of band position, previous articles

have extensively described a negative shift to a lower frequency as being indicative of strengthening of hydrogen bonding, whereas a positive shift to higher frequency is indicative of hydrogen-bond weakening.[15] Most notably, sulfonamides typically have a strong vibrational doublet due to NH$_2$ in the region 3390–3245 cm^{-1}. Crystalline CX shows a doublet at much lower wavenumbers (3342 cm^{-1} and 3232 cm^{-1}). The lower band positioning is indicative of strong hydrogen bonding within the crystalline form of CX.[16] In
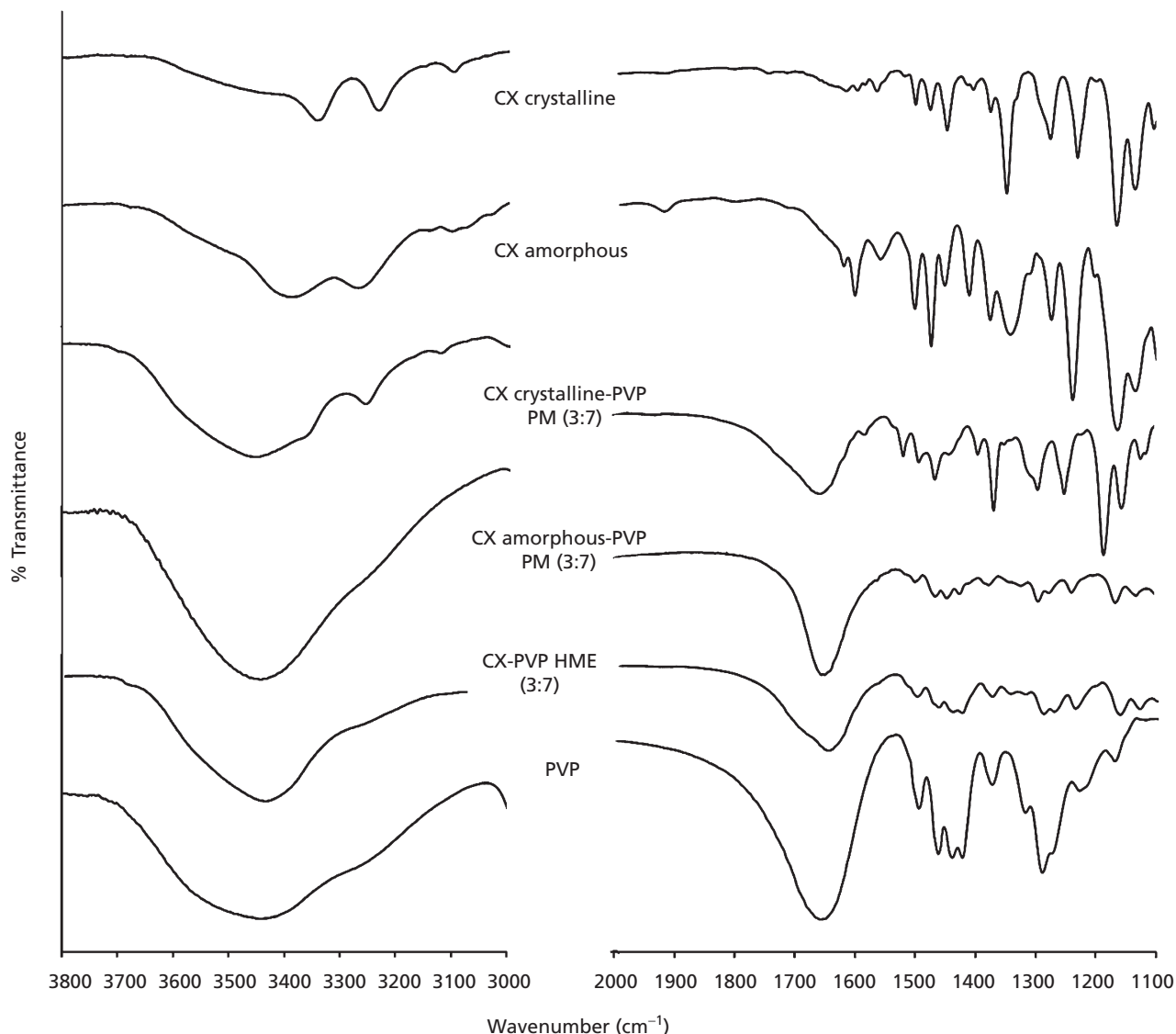
Figure 5   FTIR spectra of crystalline and amorphous CX, PVP, melt extrudates and their physical mixture. CX, celecoxib; PVP, polyvinylpyrrolidone; HME, hot-melt extruded.

Table 1   Fourier transform infrared band vibration type and position of the proton donor and acceptor groups in crystalline and amorphous CX

Vibration	Crystalline	Amorphous
N–H stretch	3342	3388
	3232	3267
N–H bend	1559	1556
S=O (stretch asym)	1347	1341
S=O (stretch sym)	1165	1163
C–F (stretch asym)	1275	1273
C–F (stretch sym)	1229	1238

asym, asymmetric; sym, symmetric.

comparison, the amorphous form of CX exhibits an NH_2 doublet that is positively shifted relative to crystalline CX (Table 1). Moreover, the symmetrical stretching vibration of C–F that occurs at 1229 cm^{-1} in the crystalline form of CX is positively shifted to 1238 cm^{-1} in the amorphous form. Both of these positive shifts are indicative of a strengthening of the N–H or C–F bonds, respectively, due to weakening or disruption of hydrogen bonding. Relative to crystalline CX, the amorphous form shows a negative shift for the SO_2 group. Although strengthening of hydrogen bonds is typically less common in the amorphous form, the negative shift observed for amorphous CX may be attributed to stronger hydrogen bonding interactions involving the oxygen atom of the SO_2 group. Strengthening of hydrogen bonds in the amorphous state has been reported previously for felodipine, nicardipine and isradipine.[15]
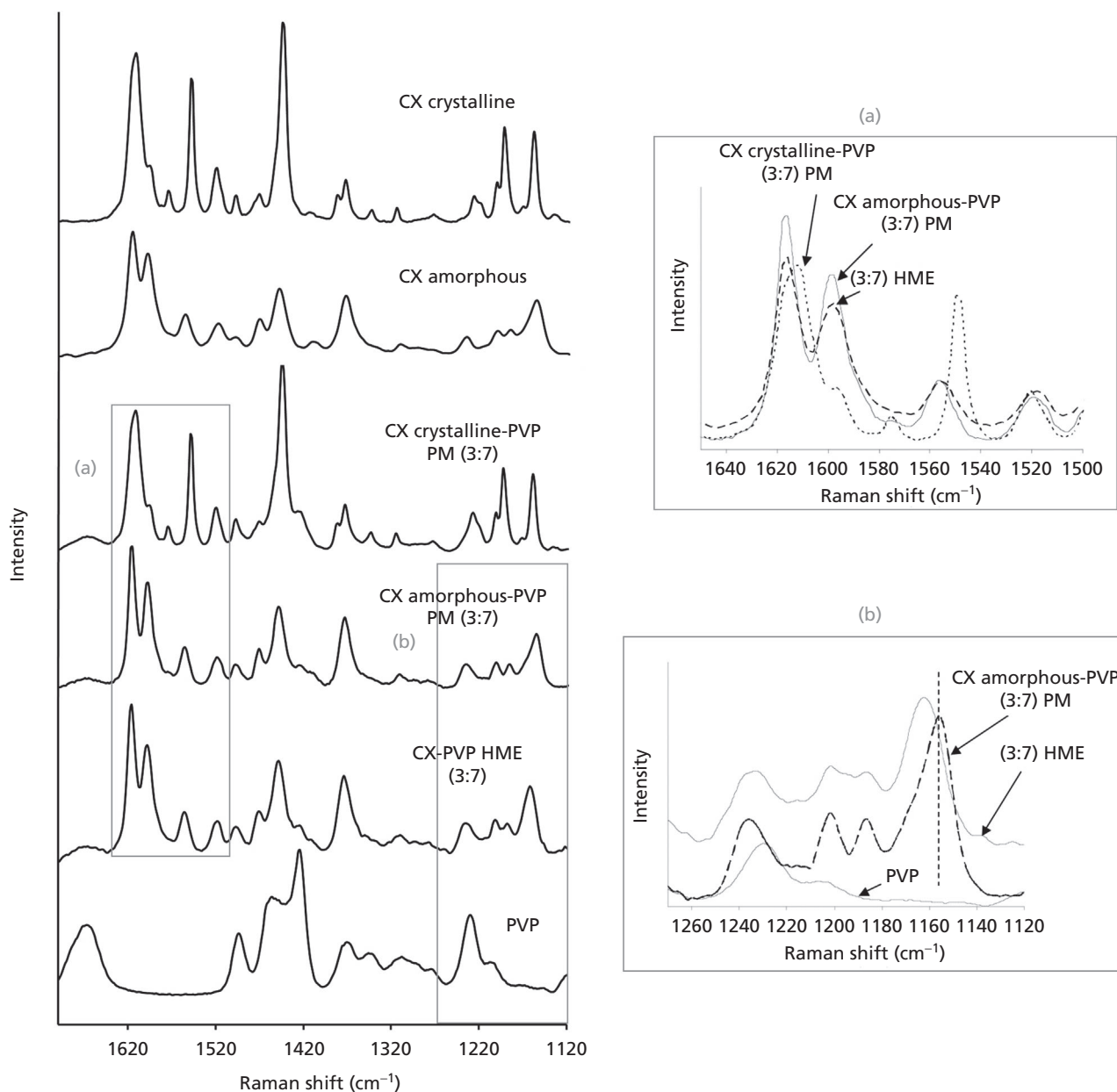
Figure 6 Raman spectra of crystalline and amorphous CX, PVP, melt extrudates and their physical mixtures. CX, celecoxib; PVP, polyvinylpyrrolidone; PM, physical mixture; HME, hot-melt extruded.

Interestingly, Raman spectroscopy identified distinct differences between the crystalline and amorphous forms of CX in relation to band shape, intensity and position (Figure 6). In particular, the peaks attributed to N–H bending and the symmetrical stretching vibrations of S=O and C–F groups were significantly broader and lower in intensity in amorphous CX than in the crystalline form. Peak broadening and lowering of intensity are often related to the high level of disorder within amorphous drug forms.[16] Whilst there was no significant shift in the N–H bending vibration, the symmetrical stretch of SO_2 within amorphous CX was negatively shifted relative to crystalline CX. Furthermore, a positive shift of the C–F group of amorphous CX to 1238 cm^{-1} was observed. These observa-

tions were in good agreement with the data obtained from FTIR spectroscopy, again providing evidence of a strengthening of hydrogen bonding interactions formed by the S=O group and a weakening in such interactions formed by C–F groups in the amorphous form of CX.

To define molecular interactions between PVP and CX post extrusion we compared the spectra of extrudates with physically mixed samples. The negative shift (−11 cm^{-1}) of the carbonyl stretch of PVP in the melt extrudates may be attributed to the hydrogen bonding interaction of this group with the NH_2 of CX. A small negative shift (−3 cm^{-1}) of the PVP carbonyl was also observed in the physically mixed sample, which may be related to secondary interactions

between the two components facilitated by physical mixing with the mortar and pestle. A similar observation has been previously reported by Forster *et al.* (2001) for physically mixed indomethacin and PVP. Exposure of the melt extrudates to $scCO_2$ had no significant effect on band position in comparison to melt extrudates pre-$scCO_2$. This suggests that the supercritical fluid remains inert and simply acts as a pore-forming agent, thus increasing the effective surface area for dissolution. It was possible to observe significant differences between the FTIR spectra recorded for extrudates and crystalline CX but not for amorphous CX. The extrudates did not show the sharp doublet associated with NH_2 stretching. This could be due to peak broadening in the amorphous form and also to the presence of a broad hydroxyl band associated with adsorbed moisture. This was also true of amorphous CX physically mixed with PVP. Conversely, crystalline CX physically mixed with PVP did display a doublet in the NH_2 region. Given the distinct similarity between amorphous CX physically mixed with PVP and melt extrudates it may be suggested that CX exists in the amorphous form within the extruded samples. Interestingly, in the FTIR spectra of melt extrudates, there is a shift in the position of the carbonyl group of PVP relative to its position within amorphous CX physically mixed with PVP. This may be indicative of the presence of strong hydrogen bonding interactions that are lengthening the C=O bond. A significant negative shift in the position of the carbonyl group of *N*-methyl-2-pyrrolidone, a structural analogue to *N*-vinylpyrrolidone, was observed using FTIR in a CX–NMP binary system.[12] In the same study, it was confirmed using molecular modelling that the red shift could be attributed to secondary interactions between CX and NMP due to the hydrogen bonding between the C=O group of NMP and the N–H group of CX.

In general, Raman spectra of the physical mixtures containing crystalline CX were similar to the Raman spectrum of crystalline CX, whereas physically mixed samples containing amorphous CX and melt extrudates showed spectra that were similar to the Raman spectrum of amorphous CX. One small difference between the extruded samples and amorphous CX physically mixed with PVP was the subtle positive shift of the S=O group from $1155 \, cm^{-1}$ to $1164 \, cm^{-1}$. The positive shift for the symmetrical S=O vibrations within the HME is indicative of a strengthening of the S=O bond and weakening of secondary interactions in which it may be involved. Previously it has been reported that the amide C=O of PVP can act as a stronger proton acceptor than a sulfonyl functional group.[17] The observed spectral differences may therefore be attributed to loss of CX–CX hydrogen bonding interactions involving the S=O and N–H groups and formation of cohesive CX–PVP hydrogen bonds involving the C=O of PVP and the N–H of CX. In so doing, the S=O would lessen involvement in secondary interaction since the C=O of PVP would now act as a proton acceptor and N–H as a proton donor. This would cause a positive shift (higher wavenumber) of the S=O bond of CX within the extrudates as the bond length decreases.

The formulation of poorly water-soluble drugs intended for oral administration as solid dispersions represents an attractive method of increasing the solubility and hence oral bioavailability of such compounds. In this study we had the aim of producing an extruded glass solution of CX, using PVP

to enhance drug solubility. In general, HME tablets have a dense structure with low porosity, which may slow the release of drug from the polymeric matrix. This delay in drug release might consequently result in a reduction of drug bioavailability and thus therapeutic response. In this study, therefore, we examined the effect of $scCO_2$ as a pore-forming agent and determined the effect $scCO_2$ had on the drug-release properties. For pharmaceutical applications, $scCO_2$ is ideal because of its relatively mild critical temperature. Supercritical conditions are easily attained ($T = 304.15 \, K$, $P = 7.38 \, MPa$) and can be removed by simple depressurization. Furthermore, $scCO_2$ is non-toxic, chemically inert, non-flammable, relatively inexpensive and easily recycled. It is well known that carbon dioxide can act as a plasticizer and has previously been shown to reduce the T_g of a number of amorphous and semi-crystalline polymers, either by being absorbed between the polymer chains, causing an increase in free volume and a decrease of chain entanglement, or by acting as a molecular lubricant that reduces melt viscosity.[18] For this reason, the combination of pressurized gases with hot-melt extrusion has received increasing attention in the polymer industry in the last decade.[19] The T_g values of melt extrudates were unchanged after exposure to $scCO_2$ ($131.1 \pm 0.3°C$). This was most probably due to the rapid diffusion of $scCO_2$ from the extrudates following depressurization of the chamber. Furthermore, the X-ray powder diffractograms obtained for melt extrudates post $scCO_2$ exposure were identical to pre-exposed samples. This suggests that CX was retained in the amorphous form and that $scCO_2$ was acting as an inert pore-forming substance. The inert nature of $scCO_2$ was further confirmed using FTIR and Raman spectroscopy. Both techniques showed that spectra pre and post exposure to $scCO_2$ were identical (data not shown).

It has been previously reported that solid dispersions are highly efficient in enhancing the dissolution properties of poorly soluble drugs (BCS class II drugs) and hence improving oral bioavailability.[20] In a recent study, in-vivo studies using a dog model confirmed that a PVP melt extrudate of a model BCS class II drug provided a sevenfold increase in bioavailability in comparison to a control formulation consisting of crystalline drug triturated with poloxamer 188.[21] In this study, in-vitro drug-release studies were conducted using simulated gastric fluid (pH 1.2) without pepsin. The gastric fluid did contain 0.1% (w/v) Triton X-100, to create a surface tension close to that of in-vivo gastric fluid.[22] Figure 7 shows the in-vitro drug dissolution profiles of HME tablets, milled extrudates (drug–polymer ratio of 3 : 7) with and without exposure to $scCO_2$, crystalline CX and the corresponding physical mixture of CX and PVP. Crystalline CX and the physical mixture of CX and PVP showed a distinct plateau at levels less than 100% release. Crystalline CX had an equilibrium solubility of $68.04 \pm 3.23\%$ (68.04 μg/ml). Interestingly, a physical mixture of PVP and CX showed an increased solubility of CX. This may be attributed to the increased wettability of the drug due to the presence of PVP.[23] The dissolution of CX from a physical mixture was rapid, whereas when it was formulated in a melt extrudate release was significantly retarded. The thermal treatment of amorphous polymers has been shown to decrease polymer free volume.[24] During extrusion, PVP is softened and subjected to intense
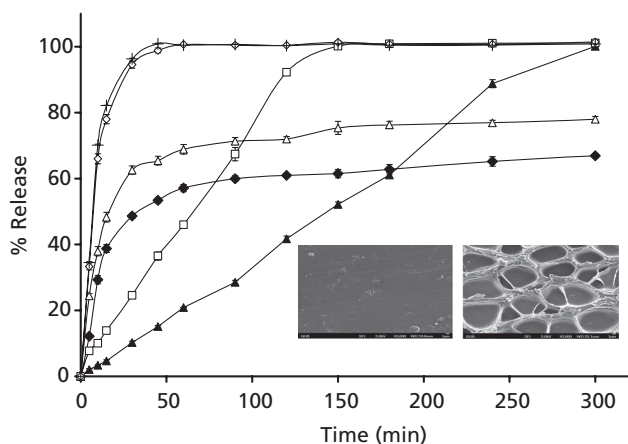
Figure 7 Dissolution profiles of crystalline CX (◆), CX crystalline-PVP (PM) (△), CX-PVP hot-melt extruded (HME) tablets without scCO₂ exposure (▲), HME tablets after scCO₂ exposure (□), milled HME without scCO₂ exposure (◇), milled HME after scCO₂ exposure (+), immediately after manufacture. The data shown are the average of three replicates and in all cases the coefficient of variance was <6%.

mixing, resulting in generation of high pressures. Air present in the polymer matrix can be excluded from the polymer melt during HME and as a result HME dosage forms are expected to have a low porosity. Thus, although CX may have been present in the amorphous form within extruded samples, drug-release rates are decreased by matrix density. As expected, the morphologies of the melt extrudates pre and post $scCO_2$ exposure were significantly different. Scanning electron micrographs showed that melt extrudates prior to $scCO_2$ exposure had a smooth surface, whereas post $scCO_2$ exposure extrudates were highly porous. These results indicate that $scCO_2$ acts efficiently as a foaming agent without affecting the solid-state properties of CX. The mechanism by which $scCO_2$ creates a foamed structure may be explained by the high diffusivity of the supercritical fluid, which enables it to penetrate efficiently through the melt extrudates. Once depressurization occurs, CO_2 rapidly expands within the pressure chamber, creating pores within the structure of the solid extrudate.[25] The increased porosity of extrudates post-$scCO_2$ exposure resulted in a significant enhancement of drug release. This may be attributed to the increased surface area available to the dissolution medium and hence faster penetration rate of the dissolution fluid. To confirm that the increase in the release of CX was related to increased surface area, extrudates pre and post $scCO_2$ exposure were milled and the fraction less than 355 μm was used for dissolution testing. In both milled samples, there was no difference in the drug-release properties, confirming a surface area effect on dissolution. The formation of solid dispersions is known to dramatically increase dissolution rate and apparent solubility, but such systems are inherently unstable.[26] Using PXRD, we have shown that extrudates containing CX : PVP at ratios of 1 : 1 and 3 : 7 are stable for periods of up to 3 months at 40°C and 75% RH. Drug-release properties of HME tablets stored under identical conditions show similar release profiles to those samples tested immediately following manufacture.

This can be attributed to the retention of CX in the amorphous form during storage.

Conclusions

HME of CX with PVP resulted in the formation of glass solutions exhibiting a single T_g and an amorphous halo in PXRD patterns. The T_g values of all melt extrudates were significantly higher than those of amorphous CX. Amorphous CX recrystallized during heating in a DSC pan whereas none of the extrudates recrystallized during heating. A strong interaction between PVP and CX was confirmed by the difference between theoretical and experimental T_g values using the Gordon–Taylor equation. FTIR and Raman spectroscopy confirmed secondary hydrogen bonding, further supporting the data obtained from DSC and PXRD. The storage stability at 40°C and 75% RH was shown to be dependent on the drug loading in the extruded matrix. Samples containing higher drug loads were less stable, which may be ascribed to a decreased T_g. An increase in equilibrium drug solubility for melt extrudates was observed but the release rate was prolonged (5 h). Exposure of extrudates to $scCO_2$ or milling samples enhanced the drug-release rate. This effect was attributed to an increased surface area.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

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