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Preparation of glass solutions of three poorly water soluble drugs by spray drying, melt extrusion and ball milling

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Abstract

The aim of this study was to investigate the influence of the manufacturing process on the physicochemical properties of three poorly water soluble compounds (carbamazepine, dipyridamole, and indomethacin) when processed with a polymer (polyvinylpyrrolidone K30 (PVP)) at a 1:2 drug to polymer ratio. Melt extrusion, spray drying, and ball milling techniques were used to prepare glass solutions. Product homogeneity, dissolution, physical stability, and drug/polymer interactions were investigated. Particular attention was paid to solid phase analysis using XRPD, modulated temperature DSC, optical microscopy, and Raman microscopy and the importance of using a combination of techniques was demonstrated. The latter technique when applied to freshly ball milled samples exhibited the presence of drug and polymer rich areas, indicating that complete glass solution formation had not occurred. The three compounds produced products with differing physical stability with indomethacin proving the most physically stable. These differences in physical stability were attributed to hydrogen bonding of drug and polymer. The manufacturing technique did not influence physical stability, but it did affect dissolution. The dissolution of the spray-dried material was generally poor, compared to melt extruded and ball milled products. This was probably due to rapid dissolution of PVP from the small particles of the spray-dried products.
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Keywords: Glass solutions; Spray drying; Milling; Melt extrusion; Indomethacin; Carbamazepine; Dipyridamole; Poly(vinylpyrrolidone)

1. Introduction

For an orally administered drug to get into systemic circulation, it must be sufficiently soluble to dissolve in the gastro-intestinal fluid. Once the drug has dissolved it must then be sufficiently permeable to be absorbed across the gastro-intestinal wall. Poorly soluble drugs may benefit from formulation approaches that overcome poor solubility and dissolution rate limited bioavailability. The solubility of a compound in the amorphous form is higher than in the more stable crystalline form because the Gibbs free energy is higher (Martin, 1993). The dissolution rate of an amorphous compound is improved relative to the crystalline form and it can be further improved if the amorphous compound is dispersed in a hydrophilic polymer. An example of this approach is the use of a glass solution (glass is defined in this paper as an amorphous solid at temperatures below its glass transition temperature), where the solute (drug) is dispersed in the solid solvent (polymer) on a molecular level. This results in a single homogeneous amorphous phase. A glass solution can also enable the formulation of an amorphous drug as it may overcome physical and chemical stability problems often associated with the amorphous state. Although glass solutions are likely to offer significant improvements in physical stability compared to neat amorphous drug, there is still potential for recrystallization. Concern over inadequate physical stability is the main factor limiting the widespread use of glass solutions.

As a consequence of their potential to improve oral bioavailability, the use of glass solutions in the formulation of poorly soluble oral compounds has been studied intensively over the last 40 years (Chiou and Reigelman, 1971; Serajuddin, 1999; Ford, 1986). The limited number of marketed glass solution products indicates that in spite of the large amount of research conducted in this area, significant gaps in the understanding

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of the properties of these products remain. One of the areas of research that has not received sufficient attention is the relevance of the manufacturing technique used to prepare the glass solution and most importantly, the influence the manufacturing technique has on the physicochemical properties of the product. Preparation of glass solutions commonly involves either thermal methods, such as melt extrusion (Forster et al., 2001) or solvent methods, such as spray drying (Corrigan et al., 1985). In comparison, high-energy milling approaches have received less attention in the literature, but have been shown to potentially result in glass solutions (Boldyrev et al., 1994) or form regions of drug/excipient miscibility (Friedrich et al., 2005). Significant questions remain as to whether or not this approach can be used to prepare glass solutions of other drugs and whether the physical properties and stability of milled systems differ from glass solutions prepared by melt extrusion or spray drying.

The aim of this study was to investigate the influence of the manufacturing process used to prepare glass solutions on the physicochemical properties of the products. Parameters of particular importance were product homogeneity, dissolution, physical stability, and drug/polymer interactions. To allow comparisons to be made between manufacturing techniques, the following study constraints were implemented. Only one polymer, poly(vinylpyrrolidone) K30 (PVP), was selected for use with all three manufacturing techniques. PVP was selected as it has high aqueous solubility, a high glass transition temperature, is miscible with a range of poorly soluble drugs, and forms hydrogen bonds with certain drugs (Forster et al., 2001). Hydrogen bonding is widely recognized as an important mechanism to increase amorphous stability (Matsumoto and Zografi, 1999). All products were prepared at a drug/PVP ratio of 1:2 (w/w) as this was suitable for processing using all three manufacturing techniques. Three poorly soluble compounds were selected: carbamazepine, dipyridamole and indomethacin. These compounds were also used in a previous investigation of crystalline to amorphous conversion of the pure drug (Patterson et al., 2005).

2. Materials and methods

2.1. Materials

Carbamazepine, dipyridamole and indomethacin were characterized and used as received from the supplier (Sigma–Aldrich Ltd.). All substances were of analytical grade. PVP was characterized and used as received (GlaxoSmithKline).

2.2. Spray drying

Drug and PVP (1:2 w/w, 10 g) were dissolved in 250 ml of dimethyl formamide (DMF) and spray-dried using a Büchi B-191 spray-drier. The following conditions were used for all drugs: aspirator flow: 100%, gas flow rate: 577 l/min, solution flow rate: 1.0–2.0 ml/min (DMF flow rate <25% lower explosive limit (LEL) = 5.7 ml/min), inlet temperature: 105 °C. The spray-dried products were dried in a vacuum oven over desiccant at 40 °C for 24 h and then at 55 °C for a further 24 h.

2.3. Melt extrusion

Drug and PVP blends (1:2 w/w, 300 g) were extruded using a Brabender Plasticorder PL2000 twin-screw melt extruder (diameter 3 1/4 in., L/D ratio 18). The extruder comprised four heating zones. The 'throat' (zone 1) was maintained at a temperature between 80 and 100 °C. The temperatures at which the three other zones were maintained were compound dependent: carbamazepine: zone 2: 188 °C, zone 3: 185 °C and zone 4: 185 °C. Dipyridamole: 167, 162 and 162 °C. Indomethacin: 175, 175 and 170 °C. All products were extruded at approximately 10 rpm due to the viscous nature of PVP and the choice of a 1:2 drug/PVP ratio.

2.4. Ball milling

Drug and PVP blends (1:2 w/w, 500 mg) were ball milled in a mixer mill (MM2 Mixer mill, Glen Creston Ltd.). The sample was milled at 17.5 s^{-1} in a 25 ml chamber for 120 min at 2% w/v with 2 mm × 12 mm and 6 mm × 7 mm diameter stainless steel ball bearings. The temperature of milling was not controlled.

2.5. Blending

Drug and PVP were weighed out at 1:2 w/w ratio (Mettler M3 balance), and then lightly mixed in a mortar with a spatula for 2 min.

2.6. Modulated temperature differential scanning calorimetry

A TA Instruments 2920 modulated DSC was calibrated for enthalpy and heating rate using indium and lead. Nitrogen was used as the purge gas (20 ml min^{-1}). Samples were prepared (2–5 mg), and were heated in aluminium pans with either pierced aluminium lids or hermetically sealed. All samples were equilibrated at 0 °C before heating. Heating rate and modulation parameters were compound dependent with the parameters chosen in order to ensure separation of the reversing and non reversing components: carbamazepine and indomethacin ±0.42 °C/80 s at 2 °C/min; dipyridamole ±0.53 °C/40 s at 5 °C/min. All measurements were carried out in duplicate and results analyzed using Universal Analysis 2000 software.

2.7. High speed differential scanning calorimetry

A Perkin-Elmer Pyris 1 DSC with helium purge gas (20 ml/min) was used to heat samples (0.2–0.5 mg) in aluminium pans with pierced lids (TA Instruments). Samples were heated from 20 to 350 °C at a nominal heating rate of 300 °C/min. The heating rate is only approximate, as temperature and enthalpy—however this calibration using indium and lead were carried out at 10 K/min heating rate. For quantitative work, a standard curve of crystalline drug in PVP was prepared by plotting the drug melting enthalpy as a function of the crystalline content. Since construction of the calibration curve required weighing small masses and potentially mixing amorphous and crystalline powders, only the crystalline material was weighed

and added directly to the DSC pan. The amorphous content was inferred by difference.

2.8. Thermogravimetric analysis

A TA Instruments Hi-Res TGA 2950 thermogravimetric analyzer was used and calibrated for weight and temperature (alumel and nickel). Nitrogen was used as a purge gas at a flow rate of 100 ml/min; 5–10 mg samples were heated in open aluminium pans to 200 °C and data was analyzed using Universal Analysis 2000 software.

2.9. X-ray powder diffractometry

Samples were analyzed using a Phillips X'Pert X-ray diffractometer calibrated using powdered α-alumina. The source was a Cu Kα 1 tube (wavelength 1.54056 Å) at 40 kV and 50 mA. All samples were prepared by front filling a recessed silicon wafer to minimize the amount of sample used and analyzed from 2 to 45 °2θ at 0.2 °2θ/4 s. Results were analyzed using X'Pert v3.2 TDS software.

2.10. Fourier transform infrared spectroscopy

Samples were analyzed using an attenuated total reflectance (ATR) germanium crystal accessory (Avatar 360 FTIR model 360, Thermo Nicolet). The instrument was calibrated using polystyrene and spectra were recorded from 4000 to 700/cm using 64 sample/background scans and 4.0/cm resolution. All measurements were carried out in duplicate and data was analyzed using OMNIC E.S.P. v5.1 software.

2.11. Polarized light microscopy

An Olympus BX51 polarized light microscope was used. Micrographs were taken using Image ProPlus software V4.0 (Media Cybernetics) and a JVC digital camera. Drug sample was brushed onto a glass slide and dispersed in silicone oil.

2.12. Scanning electron microscopy

The samples were analyzed using a Philips XL Series, XL 30. Samples were sputter coated with gold/palladium (Agar auto sputter coater).

2.13. Raman microscopy

A Raman microscope (JY LabRam Infinity) using a 785 nm NIR laser, 2.3 μm beam diameter, 3.0 μm beam depth and confocal size of 50 μm was used. Mapping of a 100 by 140 μm region was carried out in 1 μm steps after focusing using a 100× objective. Reference spectra of both carbamazepine and PVP were obtained and discriminatory peaks were assigned to carbamazepine at 1161/cm and PVP at 930/cm.

2.14. HPLC

Analysis was carried with an Agilent 1100 series HPLC, a Phenomenex luna 3 μm C18, 150 mm × 4.6 mm column and UV analysis (280 nm). A gradient was used with initial conditions 5% 0.05% TFA in acetonitrile (A), 95% 0.05% TFA in water (B) and at 20 min A = 95% (for indomethacin, initial A was 30%). Total run time was 23 min with a flow rate of 1.0 ml/min. Carbamazepine and indomethacin were dissolved in acetonitrile/water (1:1) and dipyridamole was dissolved in 0.05% TFA acetonitrile/water (1:1).

2.15. Determination of drug/polymer ratio

A combination of HPLC and TGA was used to determine the drug/PVP ratio after spray drying. After storage, water content was determined by TGA while drug content in the sample was determined by HPLC. By subtracting the water and drug content, the weight of the polymer present and consequently, the drug/PVP ratio could be determined.

2.16. Dissolution

Dissolution testing was carried out under sink conditions at 37.5 ± 0.5 °C and 50 rpm using a USP II apparatus (VanKel). Samples were pre-wet with media (degassed phosphate buffer, pH 6.8, 0.1 M) in a scintillation vial and quickly added to the dissolution vessel immediately prior to beginning the experiment. Online UV analysis (Hewlett-Packard 8453) was used after filtering solutions through 10 μm filters (Anachem). Standard curves were prepared by dissolving drug in acetonitrile/water (1:1) (carbamazepine) or acetonitrile/pH 6.8 buffer (1:1) (dipyridamole and indomethacin). Wavelength of detection was compound specific: carbamazepine, 278–282 nm; dipyridamole, 288–292 nm and indomethacin, 262–266 nm. Analysis was carried out in triplicate.

2.17. Physical stability

Products were placed on physical stability for 1 week (25 °C/<10% relative humidity (RH), 25 °C/75% RH, and 40 °C/<10% RH) and 8 weeks (25 °C/<10% RH, 25 °C/75% RH, 40 °C/<10% RH, and 40 °C/75% RH). Approximately 300 mg of sample were stored naked in open 20 ml scintillation vials.

2.18. Estimation of product Tg using the Gordon–Taylor equation

The most common approach to predict the Tg of an amorphous one-phase dispersion is the Gordon–Taylor ideal mixing equation (GT) (Fukuoka et al., 1989). The version of GT applied in this study uses the Simha–Boyer rule, which allows K to be calculated using amorphous density and Tg values (Simha and Boyer, 1962):

$$T\mathrm{g(mix)} = \frac{[(w_1 \times T\mathrm{g}_1) + (k \times w_2 \times T\mathrm{g}_2)]}{[w_1 + (k \times w_2)]} \qquad K = \frac{\rho 1 \times T\mathrm{g}_1}{\rho 2 \times T\mathrm{g}_2}$$

3. Results

3.1. Glass solution formation: solid phase analysis

Spray drying resulted in amorphous products as assessed by XRPD, DSC, and polarized light microscopy (PLM) for all three compounds (Table 1). MTDSC showed that all spray-dried products had a single *T*g indicating complete miscibility between the drug and PVP. The experimentally determined *T*g values are listed in Table 1 along with a comparison to *T*g values calculated using the GT equation. Indomethacin and carbamazepine/PVP spray-dried products exhibited *T*g values slightly below those calculated by the GT equation, whereas the experimental *T*g value obtained for dipyridamole was higher than the calculated value. Solvent content of spray-dried products was determined and attributed to the hygroscopic nature of the PVP and residual DMF (Table 1). For dipyridamole, solvent loss was observed to be a two-step process by TGA, probably indicating the presence of both water and DMF (data not shown). DMF has a higher boiling point than water and therefore evaporates at increased temperature. HPLC analysis indicated that spray drying did not result in significant chemical degradation for carbamazepine or indomethacin. HPLC analysis of the dipyridamole/PVP product showed that some degradation had occurred (Table 1). The drug/PVP ratio was confirmed for all compounds.

Melt extrusion resulted in amorphous products as assessed by XRPD, DSC, and PLM for all three compounds (Table 1). MTDSC showed that extrusion resulted in a one phase amorphous product with a single *T*g for all compounds (Table 1). The *T*g values obtained from the melt extruded samples were similar to those of the spray-dried products. The *T*g value obtained for the indomethacin/PVP melt extrudate was around 3 °C lower than that of the spray-dried material, but this may be explained by the 3.5% degradation of indomethacin detected in the sample using HPLC (Table 1). Chemical purity was also slightly lower for melt extruded carbamazepine, whereas the spray-dried dipyridamole product was thermally stable (Table 1). Performing melt extrusion at a drug/PVP ratio of 1:2 resulted in some processing difficulties. Due to the high viscosity of the product, the extrusion process initially had to be conducted at a low process screw speed and at temperatures in excess of 150 °C. PVP has been shown to degrade when kept at temperatures greater than 150 °C for prolonged periods (Wade and Weller, 1994). Therefore, the initial product was discarded until the processing rate was increased to 10 rpm leading to a reduction in residence time. This also resulted in lower than expected yields from the melt extrusion process.

Ball milling results were equivocal for determination of homogeneity and the nature of the solid phases compared to results for spray-dried and melt extruded products. Analysis of drug/PVP ball milled material by XRPD and DSC indicated the products were amorphous, but distinct areas of birefringence were noted with PLM in all samples. To further investigate the amorphous nature of the product FTIR spectroscopy was used. The application of FTIR for determination of solid state form for carbamazepine, dipyridamole and indomethacin has been previously described (Patterson et al., 2005). The affect of PVP on the ability to discriminate between amorphous and crystalline drug using FTIR was assessed and did not negate use of the technique. For example, differences were observed for dipyridamole in the CH_2 region most likely attributable to the overlap of drug and PVP C-H bands. This did not interfere with bands at 1440, 1520, and ca. 2930 cm^{-1}, which are consistent with amorphous dipyridamole (Patterson et al., 2005). For dipyridamole/PVP the absence of a band at 1440 cm^{-1} confirmed that the sample was amorphous. The spectra of indomethacin and carbamazepine/PVP ball milled samples were consistent with amorphous drug. MTDSC analysis of the ball milled samples exhibited one *T*g, providing evidence of a homogeneous product. For carbamazepine/PVP the duplicate *T*g analyses showed significant variation, a possible indication of decreased homogeneity (Table 1). It was also noted that the *T*g values obtained for the ball-milled samples were in all cases noticeably higher than those for spray-dried and melt extruded samples (Table 1).

From the above analysis it was clear that in the drug/PVP ball milled products, the drug was present in an amorphous state and that the degree of dispersion was at least approaching the molecular level. The birefringence seen with PLM was probably due to

Table 1
Characterization of drug/PVP products

Drug	Manufacturing technique	Solvent content, % w/w (+std)	XRPD	PLM	FTIR	*T*g °C, MTDSC (+std)	*T*g °C, width[a]	*T*g °C, GT	Chemical purity % (+std)	Drug/PVP ratio (+std)
Carbamazepine	SD	5.6 (0.4)	A	A	A	108 (0.3)	7.6	123	99.4 (0.2)	1:2.1 (0.0)
Dipyridamole	SD	5.6 (0.7)	A	A	A	135 (0.0)	5.1	116	98.7 (0.3)	1:2.1 (0.0)
Indomethacin	SD	6.9 (0.2)	A	A	A	111 (4.1)	13.6	115	100.0 (−)	1:2.0 (0.0)
Carbamazepine	ME	ND	A	A	A	109 (0.8)	8.5	123	97.85 (0.37)	ND
Dipyridamole	ME	ND	A	A	A	131 (0.3)	4.0	116	98.95 (0.06)	ND
Indomethacin	ME	ND	A	A	A	108 (0.4)	9.2	115	96.47 (0.03)	ND
Carbamazepine	BM	ND	A	Birefringent	A	120 (17.4)	6.7	123	ND	ND
Dipyridamole	BM	ND	A	Birefringent	A	127 (2.7)	9.0	116	ND	ND
Indomethacin	BM	ND	A	Birefringent	A	116 (9.9)	8.9	115	ND	ND

SD: spray-dried, ME: melt extruded, BM: ball milled, C: crystalline, A: amorphous, A/C: amorphous with small regions of crystallinity, A/C/C: predominantly crystalline, ND: not determined.

[a] Difference between inflection and onset temperature.

strained birefringence (Nichols, 2002). The findings of the ball milled product analysis required further investigation, as previous reports indicated the resistance of crystalline compounds to amorphous conversion by ball milling in the absence of polymer (Patterson et al., 2005). Birefringence was also observed with all ball-milled products. As with the carbamazepine/PVP sample, XRPD analysis of the products confirmed a characteristic amorphous pattern, FTIR spectra had no bands that are associated with crystalline content and HSDSC showed the absence of melt endotherms (Fig. 2). Therefore, it was concluded that ball milling all three drugs with PVP resulted in amorphous products.

In order to investigate the homogeneity of the ball milled products further, carbamazepine/PVP samples prepared using all three techniques were analyzed with dispersive Raman microscopy. Raman microscopy probes drug or polymer domains with a lateral resolution of 1 μm. The analysis generates chemical maps, which are shown in Fig. 1. All manufactured dispersions were compared to analysis of a simple physical mixture of drug and PVP prepared by lightly mixing in a mortar and pestle. The melt extruded product map was of a uniform appearance, with no evidence for drug or polymer rich domains, supporting the conclusion that this product is molecularly dispersed. The map of the spray-dried product shows the spherical morphology of the spray-dried particles and was also uniform in color, again showing further evidence of molecular dispersion. A carbamazepine rich region was identified in the spray-dried samples and was thought to be due to a small amount of recrystallization as a result of the solvent removal process post spray drying. The physical mixture clearly showed the presence of the drug and polymer domains, as expected from a heterogeneous product. The ball milled product map is predominately uniform in color, but there are small clusters of carbamazepine with a domain size of around 1 μm, approaching the limits of resolution of the Raman spectrometer, but indicating some level of heterogeneity in the product.

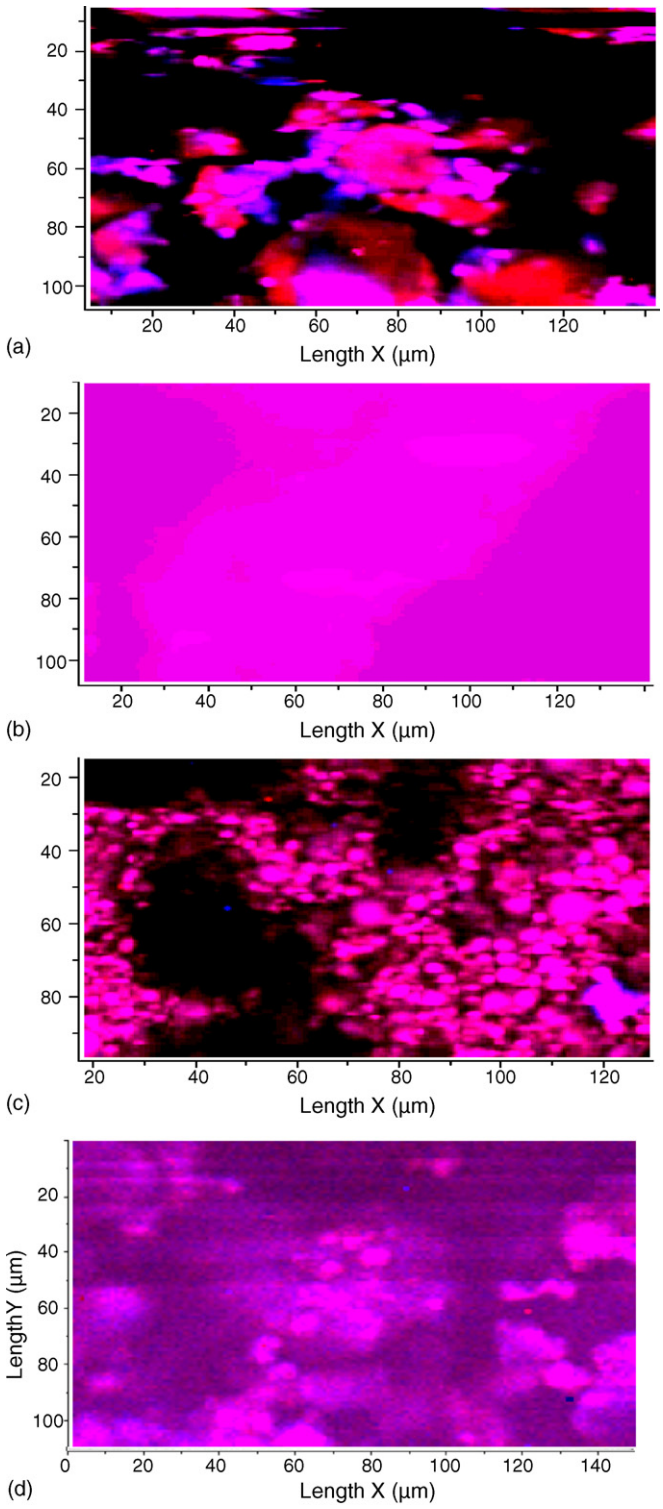

Fig. 1. Raman maps of carbamazepine/PVP (a) physical blend, (b) spray-dried, (c) melt extruded, and (d) ball milled.

3.2. Glass solution formation: drug/PVP interactions

3.2.1. Carbamazepine/PVP

FTIR spectra of all products did not show any evidence for a chemical interaction between the components (data not shown). The shift in carbonyl band position at ca.1660 cm^{-1} (vinylpyrrolidone) indicates increased conjugation, but this shift is to be expected as a result of the increased water content of the products.

3.2.2. Dipyridamole/PVP

FTIR spectra of spray-dried product gave an accurate indication of the dipyridamole/PVP interaction through PVP carbonyl band conjugation (Fig. 3). The dipyridamole moieties that would potentially interact with the PVP carbonyl group are the hydroxyl groups. It should be noted that variance in the OH stretch is difficult to determine due to insensitivity associated with the germanium ATR crystal used in these experiments. Additionally, the high water content in the hygroscopic drug/PVP further decreases the sensitivity for detecting changes in the hydroxyl group. Use of the PVP carbonyl frequency is less problematic as it is specific to PVP and therefore any decrease in the wave number of this band is indicative of carbonyl conjugation by either drug or water. Therefore, the effect of water on PVP and the influence dipyridamole dispersion on carbonyl conjugation was investigated (Fig. 4). Between 2 and 6% water content the presence of dipyridamole dispersed at a molecu-

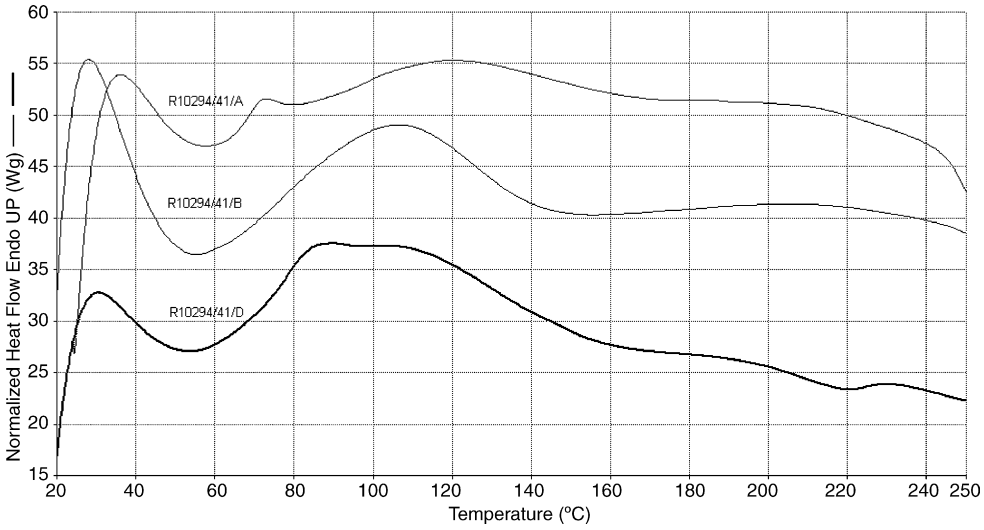

Fig. 2. HSDSC of carbamazepine/PVP milled, dipyridamole/PVP milled, and indomethacin/PVP milled (top to bottom). An endotherm in the 150–200 °C region indicates crystalline content.

lar level leads to a significant decrease in the carbonyl wave number beyond that due to water alone. This indicates the presence of hydrogen bonding between the drug and polymer for the spray-dried material. FTIR analysis of the melt extruded product showed the carbonyl band at 1662 cm^{-1}, associated with a water content of 3.6%. Using the relationship shown in Fig. 4, the influence of dipyridamole on carbonyl conjugation can be established. Without drug present, a water content of 3.6% would result in a band position of ca.1666 cm^{-1}, assuming all the water interacts with PVP and taking into account the 1:2 drug/polymer ratio (3.6/0.66 = 5.5% water in PVP). Therefore, the presence of hydrogen bonding between drug and polymer is also exhibited for the melt-extruded material.

3.2.3. Indomethacin/PVP

FTIR spectra showed evidence for hydrogen bonding between drug and PVP in samples produced using all three techniques. The mechanism of the indomethacin/PVP interaction and the influence this has on the dimer configuration of amorphous indomethacin has been reported previously (Taylor and Zografi, 1997). When formulated with PVP as a glass solution indomethacin loses the band associated with the asymmetric acid carbonyl cyclic dimer at ca. 1717 cm^{-1}. The non-hydrogen bonded carbonyl band, observed as a shoulder at 1735 cm^{-1} now appears as a discrete band at 1721 cm^{-1} as a result of the increase in free acid carbonyl associated with the loss of cyclic dimer formation. The dimer formation is lost as the hydroxyl

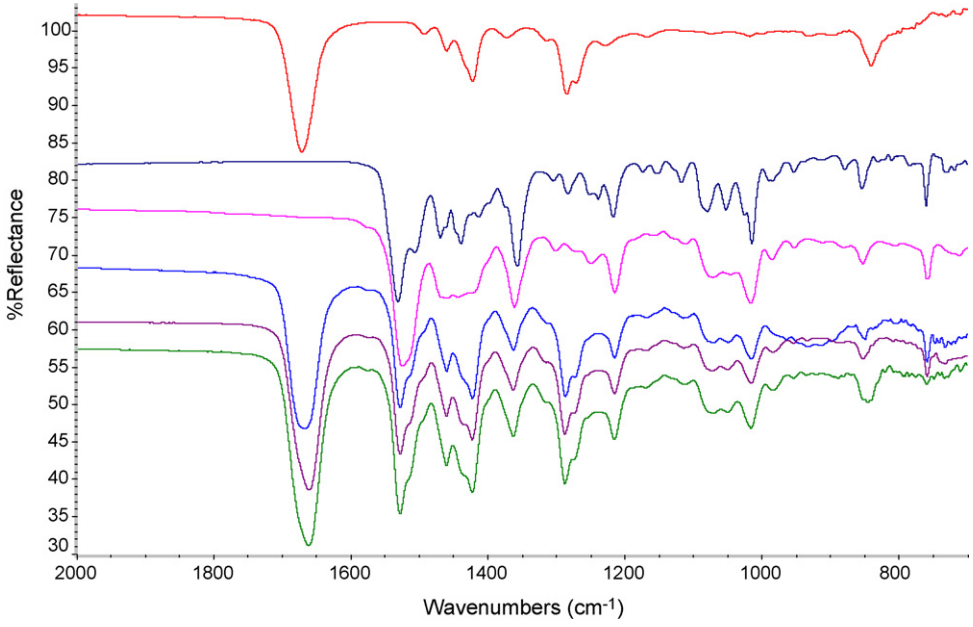

Fig. 3. FTIR of PVP K30, crystalline dipyridamole, amorphous dipyridamole, dipyridamole/PVP spray-dried, dipyridamole/PVP melt extruded, and dipyridamole/PVP ball milled (top to bottom).

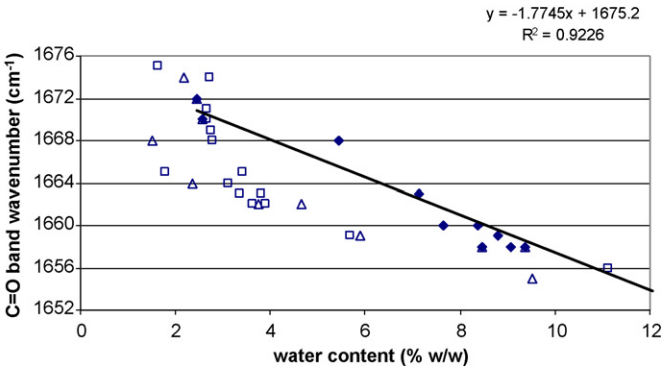

Fig. 4. Influence of dipyridamole on PVP conjugation. Solid dots indicate carbonyl wave number for neat PVP and associated trendline. Ball milled dipyridamole/PVP (open squares) and spray-dried dipyridamole/PVP (open triangles) show the influence that dipyridamole has on carbonyl conjugation.

group of the carboxylic acid preferentially binds to the PVP carbonyl (Taylor and Zografi, 1997). In spite of the conjugation with the OH group the PVP carbonyl band position remains at a high wave number. This is because at 1:2 indomethacin/PVP ratio there is an excess of PVP. A stoichiometry of 1:1 only requires 22% w/w PVP based on monomer molecular weight. Work by Taylor and Zografi (1997) confirms this hypothesis as they reported that at concentrations of PVP greater than 50%, the conjugated PVP carbonyl band is not distinct and merges with the unbound carbonyl peak.

3.3. Dissolution studies

In comparison to crystalline drug and drug/PVP physical blends, the melt extruded and ball milled products generally showed a significant increase in dissolution rate (Table 2). Compared to a physical blend both melt extruded and ball milled dipyridamole products exhibited around a two-fold increase in dissolution after 60 min while spray-dried product exhibited smaller increases. With indomethacin products spray drying, ball milling, and melt extrusion resulted in a >two-fold increase in dissolution at 60 min compared with the physical blend, with even greater gains in the first 10 min of dissolution. Whilst the dissolution profiles for all the ball milled and melt extruded products were similar, the dissolution profiles of the spray-dried products were found to be compound specific and exhibited significantly less improvement in dissolution rate and extent compared to physical blends. This decreased dissolution per-

Table 2
Dissolution data

Drug	Manufacturing technique	*Q*10	*Q*60	Dissolution rate increase compared to PM	
				*Q*10	*Q*60
Carbamazepine	SD	53.6 (6.3)	73.8 (5.7)	0.8	0.8
Dipyridamole	SD	66.2 (1.3)	69.0 (1.3)	1.8	1.4
Indomethacin	SD	89.4 (4.0)	90.6 (4.6)	5.0	2.1
Carbamazepine	ME	84.6 (0.3)	88.4 (1.1)	1.2	1.0
Dipyridamole	ME	90.5 (2.3)	91.8 (2.3)	2.4	1.8
Indomethacin	ME	99.0 (3.6)	99.5 (3.6)	5.0	2.4
Carbamazepine	BM	93.2 (4.9)	94.3 (4.8)	1.3	1.0
Dipyridamole	BM	77.3 (2.1)	85.1 (2.9)	2.1	1.7
Indomethacin	BM	102.4 (4.3)	103.0 (4.3)	5.1	2.4
Carbamazepine	PM	70.4 (2.0)	92.8 (2.1)	1.0	1.0
Dipyridamole	PM	37.7 (4.4)	49.9 (4.5)	1.0	1.0
Indomethacin	PM	19.9 (5.0)	42.2 (8.6)	1.0	1.0
Carbamazepine	Crystalline drug	44.3 (13.5)	58.9 (12.5)	0.6	0.6
Dipyridamole	Crystalline drug	15.7 (5.7)	19.0 (3.6)	0.4	0.4
Indomethacin	Crystalline drug	35.8 (2.2)	67.1 (6.7)	1.8	1.6

Where *Q*10, *Q*15, and *Q*60 equal percent drug release after 10 and 60 min, respectively (values in brackets show standard deviation).

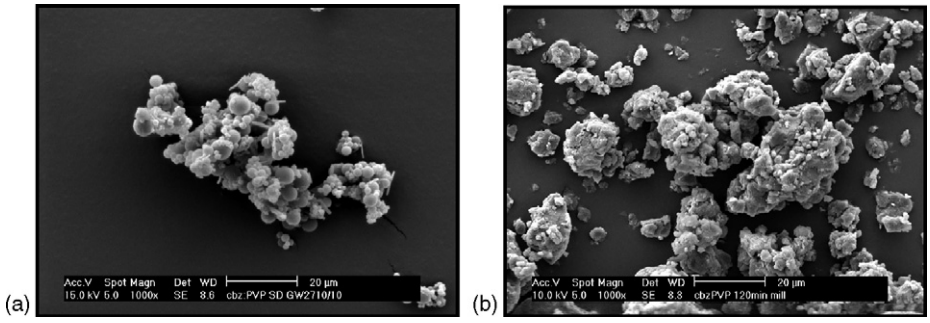

Fig. 5. SEM of carbamazepine/PVP (a) spray-dried, (b) ball milled.

formance was most noticeable for carbamazepine. Spray-dried indomethacin dissolution performance was equivalent to the ball milled and melt extruded products. Spray-dried dipyridamole showed an improvement in dissolution rate in comparison to the physical blend over the initial 10 min but after 60 min drug release was lower than the ball milled and extruded products and similar to the physical blend. Spray-dried carbamazepine actually showed decreased dissolution rate and extent in comparison to the physical mixture over 60 min. All the spray-dried samples were observed to disperse well in the media during testing with no evidence of material floating or forming a solid plug at the bottom of the dissolution vessel. However, the spray-dried material appeared to form large secondary agglomerates during the test. Therefore, the decreased dissolution rate cannot be attributed to initial non-wetting of the sample, but potentially a change in the wetting characteristics during the dissolution. The particle size of material was analyzed by microscopy with spray-dried products exhibiting the smallest particle size (Fig. 5).

3.4. Glass solution physical stability

The results from the physical stability study are shown in Table 3. A product was considered physically stable when it was shown to be amorphous when analyzed by XRPD, FTIR, and PLM. Carbamazepine/PVP products were the least physically stable, whereas indomethacin/PVP products showed the highest physical stability. Even under accelerated ICH (Q1A) conditions of 40 °C/75% RH, indomethacin/PVP products remained amorphous. For the carbamazepine products there was no apparent difference in the physical stability of products prepared with spray drying, melt extrusion, or ball milling. For dipyridamole, the extent of recrystallization seen was lower than for, even at the accelerated condition. Unlike both carbamazepine and indomethacin, at 75% RH all dipyridamole products formed coalesced masses, making certain physical analysis problematic. Dipyridamole products also typically had higher water contents after storage compared to the other drug formulations (Table 3).

The effect of water on the stability and *T*g values of the products was further investigated using MTDSC with analysis performed with non-hermetically sealed pans. The physical stability samples stored at 75% RH showed some evidence of platicization however, this was not pronounced as water evaporated during analysis (Table 3). Carbamazepine/PVP stability samples stored at high RH showed an increase in *T*g when analyzed by DSC in non-hermetic pans (data not shown). This can also be attributed to the increased water content facilitating carbamazepine recrystallization. As carbamazepine recrystallizes, there is less amorphous drug to plasticize the PVP and hence the product *T*g approaches that of neat PVP (Patterson et al., 2003). MTDSC indicated carbamazepine recrystallization by *T*g elevation (Table 3). In spite of the presence of crystalline drug and elevation of product *T*g, no melt endotherm was observed by MTDSC. Raman mapping of the samples stored under dry conditions (<10% RH) confirmed that the samples remained amorphous (Fig. 6). Raman mapping of the carbamazepine/PVP extrudate samples stored at elevated RH (75% RH) indicated that significant phase separation had occurred, but could not

Table 3
Physical stability of drug/PVP products after eight weeks storage

Drug	Manufacturing technique	25 °C/10% RH			25 °C/75% RH			40 °C/10% RH			40 °C/75% RH		
		Water, % w/w	Solid state[a]	*T*g °C, MTDSC	Water, % w/w	Solid state[a]	*T*g °C, MTDSC	Water, % w/w	Solid state[a]	*T*g °C, MTDSC	Water, % w/w	Solid state[a]	*T*g °C, MTDSC
Carbamazepine	SD	3.2	A	ND	10.3	A/C	130	3.4	A	109	10.9	C	ND
Dipyridamole	SD	3.9	A	ND	10.8	C	61	3.8	A	136	9.8	C	ND
Indomethacin	SD	3.3	A	ND	7.9	A	111	3.1	A	113	7.6	A	ND
Carbamazepine	ME	1.3	A	ND	14.2	C	127	2.3	A	109	12.7	C	ND
Dipyridamole	ME	3.3	A	ND	13.2	A/C	132	3.9	A	133	9.7	A/C	ND
Indomethacin	ME	2.1	A	ND	9.8	A	108	2.5	A	105	7.8	A	ND
Carbamazepine	BM	ND	A	ND	ND	A/C	ND	ND	A	ND	ND	ND	ND
Dipyridamole	BM	6.5	A	ND	10.9	C	128	5.5	A	125	11.0	C	ND
Indomethacin	BM	5.6	A	ND	8.5	A	109	4.5	A	108	8.4	A	ND

A: amorphous, C: crystalline, A/C: partially crystalline, ND: not determined.
[a] As determined by XRPD, FTIR, PLM.

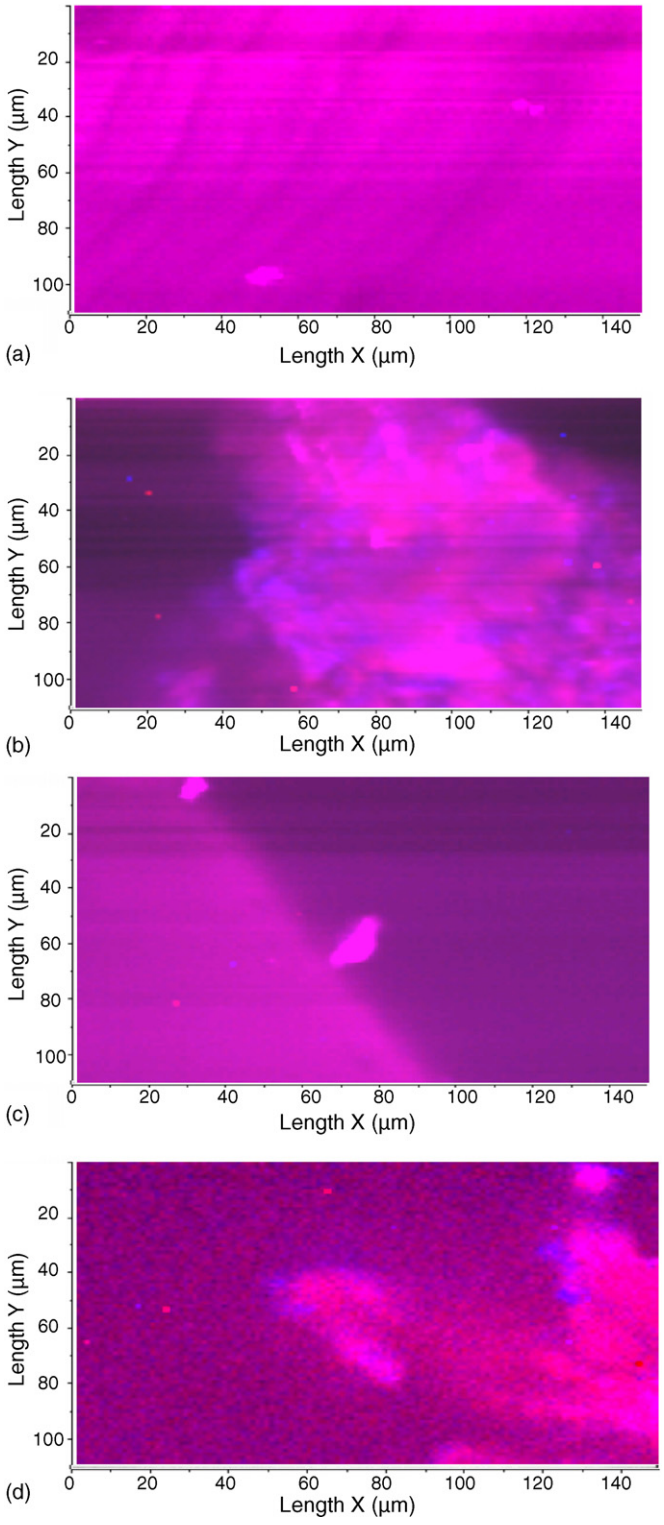

Fig. 6. Raman maps of carbamazepine/PVP melt extrudate stored for 8 weeks at (a) 25 °C/<10% RH, (b) 25 °C/75% RH, (c) 40 °C/<10% RH, and (d) 40 °C/75% RH.

be used to confirm crystallinity of the drug. HSDSC of the elevated humidity carbamazepine products did show a carbamazepine melt endotherm indicating the presence of crystalline carbamazepine (data not shown). The crystalline content was calculated to be 4 and 6% w/w for the 8 week 25 and 40 °C/75% RH samples, respectively. Verification of the HSDSC findings by FTIR and XRPD qualitatively showed that the carbamazepine extrudate product stored at high humidity had partially recrystallized to form III (appearance of bands at 3466 and 1600 cm^{-1} by FTIR—data not shown).

Table 4
Hildebrand solubility parameters

Compound	D ($MPa^{1/2}$)
Carbamazepine	24.8
Dipyridamole	29.6
Indomethacin	23.9
PVP	23.7
Sulfathiazole	26.4

4. Discussion

Ball milling is a fundamentally different method for preparing drug/polymer glass solutions than melt extrusion and spray drying. Melt extrusion and spray drying generate the amorphous product via a more highly disordered liquid amorphous phase (solution or melt), whereas using ball milling, the product should remain as a solid; changing state from a highly structured crystalline compound to the disordered amorphous state. The differences in the manufacturing technique are likely to account for some of the differences seen in the characterized products. Ball milling of carbamazepine with PVP resulted in an amorphous product. Previous carbamazepine ball milling studies showed that milling under identical conditions did not result in crystalline to amorphous conversion of the neat drug. In comparison, the same study showed that indomethacin could be converted to an amorphous form using ball milling and dipyridamole to a predominately amorphous solid (Patterson et al., 2005). The crystalline to amorphous conversion of carbamazepine in the presence of PVP cannot be due to the influence of drug/polymer hydrogen bonding as no evidence for this was found using FTIR. Therefore, amorphization of carbamazepine in the presence of PVP must be due to the degree of solubility of the drug in PVP. During the milling process, heat is generated and the crystalline carbamazepine may dissolve in the rubbery PVP. Further evidence that the components will have a degree of solid solubility is that solubility parameters of the two components are similar (Table 4). Selection of components with similar solubility parameters may provide a means by which a single amorphous phase can be predicted to form (Forster et al., 2001). This may also explain the findings of Boldyrev et al. (1994) who prepared amorphous sulfathiazole/PVP products by ball milling (Table 4). The formation of amorphous indomethacin/PVP ball milled product is not unexpected. Previous studies have shown that even light physical mixing of strongly hydrogen bonding compounds, such as ibuprofen can lead to a degree of solid solution formation (Sekizaki et al., 1995), indicating that interactions between components can increase the likelihood of molecular dispersion. These mechanisms are also likely to contribute to the formation of an amorphous dipyridamole/PVP product.

Ball milling resulted in amorphous drug, which was well dispersed as shown by single *T*g values. However, the increased width of the *T*g and changes in *T*g relative to melt extruded and spray-dried products, indicated that the degree of dispersion was more compound specific and different to that obtained by melt extrusion and spray drying. Further analysis of carbamazepine products with Raman microscopy confirmed this to be the case. Raman mapping of the carbamazepine/PVP physical blend showed that simple mixing of the two components did not result in a homogeneous product. Analyses of the melt extruded and spray-dried products showed that these preparative techniques resulted in a completely homogeneous product. The small carbamazepine rich region observed in the spray-dried sample is likely to be attributable to the solvent removal step leading to a localized recrystallization event. In comparison, Raman maps of the ball milled product, although appearing to be relatively homogeneous, show evidence for small clusters of carbamazepine rich areas, indicating that complete glass solution formation has not occurred. The major limitation of Raman mapping in this study was the lack of discrimination between crystalline and amorphous drug. Several products, in particular the carbamazepine stability samples demonstrated the absence of a melt endotherm by MTDSC, but showed evidence for crystalline drug by XRPD and FTIR. In addition, the physical state of the samples stored at 75% RH made analysis difficult, especially using XRPD, with the requirements of forming a flat, lightly compressed sample surface. HSDSC has proved useful for both qualitative and quantitative analysis of crystallinity. Using conventional heating rates there is the chance that the glass solution may reform on heating leading to an absence of a drug melt peak for a product containing crystalline drug. This can be overcome by taking advantage of the high heating rates of HSDSC.

Friedrich et al. (2005) reported that nifedipine formed dispersed amorphous drug powders with PVP and HPMC following up to 120 min grinding with a metal ball mill and a drug/polymer ratio of 1:3. However, the XRPD patterns shown in the study clearly demonstrate that the drugs, though markedly less crystalline, retain a degree of crystallinity. It has been previously shown that nifedipine forms glass solutions when melt extruded with PVP at a 1:1 ratio and additionally, that the components interact by hydrogen bonding (Forster et al., 2001). Based on the findings from this study, it would be reasonable to expect nifedipine to also form a highly dispersed amorphous drug/polymer product using ball milling. The fact that Friedrich et al. did not achieve this type of product reflects the inconsistency of ball milling approaches and the contribution that differences in milling frequency, material loading, number and size of milling media can contribute to differences in the product formed.

The extent of deviation in the glass solution *T*g from that predicted by the GT equation was compound specific. Irrespective of preparative technique, the carbamazepine/PVP products showed negative deviation from the GT (Fig. 7). In comparison, the indomethacin glass solutions demonstrated a slight negative deviation for melt extruded and spray-dried products. Dipyridamole/PVP products on the other hand, exhibited a positive deviation from the theoretical values calculated. For carbamazepine and indomethacin products, the higher *T*g values obtained with ball-milled samples may indicate the presence of PVP rich areas. For dipyridamole this was not the case. Previous investigations into the *T*g of glass solutions have either shown values in agreement with those calculated using the GT equation or a negative deviation (Forster et al., 2001; Taylor and Zografi, 1998). Taylor and Zografi (1998) investigated the behavior of sugar/PVP glass solutions and found that the choice of sugar influenced the extent of the negative deviation in the *T*g. The authors used FT-Raman spectroscopy to investigate the effect that glass solution formation had on conjugation of the PVP carbonyl group. They concluded that negative deviation in the *T*g occurred as a result of the PVP carbonyl acting as a proton acceptor in preference to the intramolecular hydrogen bonds that existed in the neat sugar. This caused the strength and/or number of the subsequent sugar/PVP hydrogen bonds to be significantly less than the self-association of sugar molecules leading to a decreased *T*g. The relationship between intermolecular bonding and subsequent glass solution *T*g can be used to explain the positive and negative deviations reported for the glass solutions presented in this study. Crystalline and amorphous carbamazepine exist as dimers and the neat drug has strong self association. As a result of carbamazepine existing in this configuration, the ability of the NH_2 moiety of carbamazepine to hydrogen bond with the carbonyl group of PVP is minimized, because one hydrogen is already bound with a carbonyl moiety of a neighbor. When a carbamazepine/PVP glass solution is prepared, the PVP carbonyl group must compete for hydrogens from the carbamazepine amine group. No evidence for a carbamazepine/PVP interaction was detected with FTIR. However, the presence of PVP may interrupt the formation of molecular dimers if a molecular dispersion forms. Katzhendler et al. (1998) proposed that carbamazepine may be able to interact with polymers that are capable of hydrogen bond donation, but this is not possible with PVP.

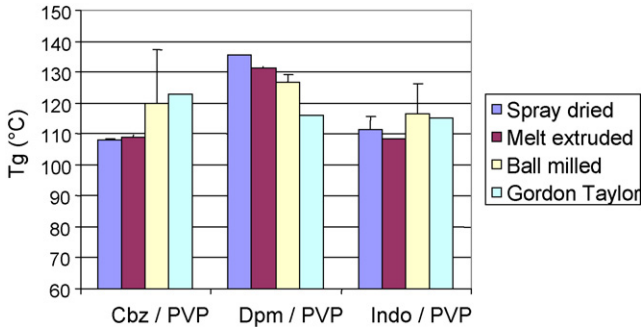

Fig. 7. Influence of preparative technique on the *T*g of glass solutions.

Dipyridamole has four potential sites per molecule from which it can hydrogen bond to PVP. The dipyridamole molecule does not have sufficient proton acceptor groups and only limited self-association can be expected. FTIR studies of the PVP carbonyl band frequency in the presence of dipyridamole suggested that significant interaction occurs (Fig. 4). The increase in *T*g relative to the GT demonstrates that hydrogen bonding of dipyridamole and PVP increases the intermolecular hydrogen bonding network in comparison to drug alone. The indomethacin/PVP

product shows a small negative deviation in *T*g even though significant hydrogen bonding between the components was detected. This difference in *T*g behavior compared to the dipyridamole products is hypothesized to be a result of the hydrogen bonding that occurs in neat amorphous indomethacin. Both neat indomethacin and indomethacin/PVP systems have hydrogen bonds whereas neat amorphous dipyridamole does not. Therefore, for dipyridamole the formation of a product with hydrogen bonds results in the observed positive deviation.

The method of preparing the solid dispersion resulted in differences in the extent of deviation from the GT predicted *T*g. The spray-dried and melt extruded carbamazepine/PVP products showed greater negative deviation than the ball milled product. The dipyridamole/PVP products showed the greatest positive deviation when prepared by spray drying and melt extrusion compared to ball milling. These findings helped to confirm that spray drying and melt extrusion facilitate better mixing than ball milling, thereby allowing greater opportunity drug/PVP hydrogen bonding.

Currently, the best approach for determining the extent of drug/polymer interaction is to use deviation from ideal mixing. The *T*g findings regarding influence of preparative technique are particularly interesting since FTIR spectra of the carbamazepine/PVP and dipyridamole/PVP products were unable to differentiate between preparative techniques with respect to the strength or extent of hydrogen bonding. However, a major issue with using the *T*g approach for discrimination is the accuracy of experimental *T*g determination using DSC, as the input of thermal energy may facilitate unwanted physical change, especially at conventional heating rates. A glass solution will have a single *T*g at a temperature intermediate to that of the individual components. The 'width' of the *T*g (between onset temperature of *T*g and temperature of inflection) is often overlooked in experimental studies and may provide an indication of product homogeneity as regions of differing drug/polymer concentrations may occur. A broad *T*g may indicate that there are heterogeneous regions within the amorphous product or that chemical degradation has resulted in by-products that act as plasticizers. This may have occurred with the melt extruded indomethacin product, which exhibited 3.5% degradation. Previous work has shown that decomposition products can have a significant effect on the experimentally measured *T*g, changing the value by as much as 20 °C for amorphous glibenclamide prepared using quenching cooling of the melt (Patterson et al., 2005). Table 1 shows the width of *T*g values of products prepared by the three different preparative techniques. Melt extruded products had the smallest *T*g width while the width of the spray-dried and ball milled products were very similar (Table 1). These results indicate that the melt extrudates are the most homogeneous products.

Previous studies, such as that by Van Drooge et al. (2006), have relied on the presence of a single *T*g to indicate that a molecular dispersion has been achieved. In this study for samples with multiple *T*g values, water vapor sorption studies were used to establish the cluster size of drug domains, which were reported to be in the region of 10–20 nm. This size of domain would be impossible to detect using Raman microscopy alone. However, Raman mapping has been shown in this study to be a useful method to determine the homogeneity of a glass solution. Compared to MTDSC, Raman analysis imparts minimal energy into the sample and is, therefore, less likely to cause a change in the solid state of the samples (Breitenbach et al., 1999). However, studies with atomic force microscopy or time-of-flight secondary ion mass spectroscopy would provide improved resolution and could be considered for future studies.

Physical stability studies of the carbamazepine product resulted in two findings. Firstly, the manufacturing technique did not influence physical stability and secondly, that a lack of drug/polymer hydrogen bonding resulted in a comparatively unstable amorphous product (Table 3). The lack of variation in physical stability on the basis of preparative technique was irrespective of the deviation in *T*g observed between the different preparative techniques and the presence of drug domains in the ball milled samples. In comparison to the unstable carbamazepine/PVP products, both dipyridamole and indomethacin have been shown to be capable of hydrogen bonding with the PVP via the carbonyl group. Evidence of partial recrystallization was observed for the dipyridamole products when stored at high relative humidity. However, this may be due to the inherent physical instability of amorphous dipyridamole, which was the most unstable of the three compounds when converted to the amorphous form by quench cooling of the melt (Patterson et al., 2005). Irrespective of the decreased amorphous stability, the extent of recrystallization observed was less than that seen for the carbamazepine/PVP products. The decrease in dipyridamole physical stability at high humidity may also be a result of the product absorbing a large amount of water. There are a number of well-established mechanisms by which increased water content can facilitate recrystallization. Plasticization, increased molecular mobility and competition for hydrogen binding sites lead to solid phase separation and consequent recrystallization. Unlike the carbamazepine and indomethacin products, the dipyridamole/PVP products stored at elevated RH underwent a major change in appearance changing into coalesced masses. As well as the direct plasticizing effect of water, it may also decrease the physical stability by interfering with the dipyridamole/PVP hydrogen bond by binding preferentially to PVP and/or dipyridamole.

Indomethacin showed the greatest physical stability with no recrystallization encountered at any of the storage conditions. These findings appear to contrast the *T*g deviation results with dipyridamole exhibiting the greatest positive deviation from the value predicted by the GT equation. As discussed, the greater relative positive deviation is a function of both the lack of hydrogen bonding observed in the dipyridamole molecule and also the strength of the subsequent dipyridamole/PVP interaction. In comparison, indomethacin glass solutions may not exhibit such deviation in spite of the strong indomethacin/PVP hydrogen bonding. The important parameter to be derived from the theoretical *T*g calculation and subsequent experimental deviation appears to be the absence of a negative deviation from the values predicted by the GT equation.

Storage of neat amorphous carbamazepine at high humidity had previously been shown to influence the polymorphic form to

which recrystallization occurred (Patterson et al., 2005). However, it appears that in the presence of the hygroscopic PVP, in spite of these samples absorbing a large amount of water, formation of the dihydrate was not observed by XRPD (data not shown). This finding indicates that water preferentially binds to PVP as opposed to carbamazepine. Van Drooge et al. (2006) identified the hydrophobization of PVP when a hydrophobic drug is molecularly dispersed. This is probably partly due to hydrogen bonding between the drug and PVP, limiting access of water to these sites on PVP and explains why decreased water vapor uptake is reported on studies with glass solutions compared to physical mixtures (Forster et al., 2001; Van Drooge et al., 2006).

The most significant reason for preparing drug/polymer glass solutions is to improve bioavailability by increasing the aqueous dissolution rate and extent of drug release. In this study formation of glass solutions by melt extrusion or amorphous dispersions by ball milling markedly improved the dissolution rate and extent of drug release. The reasons for this are well known, including presence of the amorphous drug, decreased drug particle size to the molecular level and the intimacy of mixing with a hydrophilic polymer (Forster et al., 2001). The dissolution of the spray-dried products was poor and there are several possible reasons for this finding. The spray-dried products had the smallest particle size when analyzed using microscopy. The combination of a small size and increased surface area may have resulted in the highly water soluble PVP dissolving very rapidly, leaving behind amorphous carbamazepine without the intimate presence of the polymer. This is likely to have resulted in rapid recrystallization of the drug and would have certainly reduced the overall dissolution rate and the wetting of the drug. Spray-dried indomethacin/PVP showed a comparable dissolution to melt extruded product, dipyridamole/PVP an initial increase and spray-dried carbamazepine/PVP dissolution was comparable to a physical mixture. This order may reflect the relative strength of hydrogen bonding between the drugs and PVP. The increase in hydrogen bonding may limit the rapid loss of PVP from the spray-dried particles due to the hydrophobization of PVP described by Van Drooge et al. (2006).

The major advantages of ball milling as a manufacturing technique are the reduction in thermal stress in comparison to techniques such as melt extrusion, and the absence of unwanted solvent, compared with spray drying. These potential benefits are of limited use however, if the process does not result in a homogeneous glass solution, although in this study the consequence of incomplete miscibility following manufacture on product physical stability was not detected. Huttenrauch et al. (1985) stated that prolonged milling could result in the product absorbing the excess free energy leading to an acceleration of both physical and chemical reactions hastening degradation. However, these effects on stability were not detected during the physical stability study described here.

5. Conclusions

Drug/polymer products prepared by spray drying and melt extrusion were shown to be physicochemically similar, but differences were observed by Raman microscopy for the ball milled carbamazepine/PVP products. Characterization of solid phase homogeneity of the products highlighted the advantages and disadvantages of a number of analytical techniques and the utility of these techniques to detect low-level crystallinity. Results showed that FTIR is often a sensitive and simple method by which crystallinity can be determined qualitatively. The physical stability study demonstrated the importance of a combination of analytical approaches to amorphous characterization and low-level crystalline content detection. MTDSC is a commonly used amorphous characterization technique although this study highlighted that the technique does have potential drawbacks through unwanted sample change during analysis, especially at low heating rates. The study indicated that preparative technique is of importance with regard to chemical stability and processing, but that choice of manufacturing approach appears to have minimal influence on physical stability. In particular the effect of having a distinct amorphous drug phase in the ball-milled material on the physical stability of the samples was not detected. However, phase separation is clearly a precursor to product instability and should be avoided, especially if the drug rich domains begin to grow in size.

The influence of hydrogen bonding on the *T*g variation observed between experimentally determined and theoretical values was most pronounced when the drug/polymer hydrogen bonding was significantly higher or lower than drug self association via inter- or intramolecular hydrogen bonds. Characterization of compound intermolecular hydrogen bonding and any influence water may exert directly or indirectly should be established. Assessment of the potential for drug/polymer interactions may help explain the experimentally determined *T*g values but will not enable prediction of the relative strength of the interactions formed or the importance of these interactions to forming the glass solution or maintaining product stability.

The aim of this work was to gain an increased understanding of the important factors to consider when using glass solutions as a formulation technique. An objective was to build on a neat drug study, which showed that the chemical stability during processing must be a primary consideration (Patterson et al., 2005). On the basis of the carbamazepine work in this study, if a compound which is unstable as a neat amorphous form does not form hydrogen bonds with the PVP then irrespective of preparative technique, development of a sufficiently stable glass solution will be difficult. However, there may be ways to overcome a lack of hydrogen bonding, such as using a polymer with an even higher *T*g, which exerts an even greater anti-plasticizing effect.

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