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# Melt Extrusion and Spray Drying of Carbamazepine and Dipyridamole with Polyvinylpyrrolidone/Vinyl Acetate Copolymers

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***Aim:*** **Carbamazepine and dipyridamole are class II compounds (BCS) whose oral bioavailability is limited by poor solubility. The use of glass solutions to improve the bioavailability of this class of compound has been an area of research for a number of years. The influence of polymer parameters ($T_g$, hydrophilicity, solubility parameter, and ability to hydrogen bond) on glass solution properties is investigated.** ***Methods:*** **Carbamazepine and dipyridamole glass solutions are prepared with PVP/VA 64 and PVP/VA 37 by spray drying and melt extrusion. The products are then characterized by XRPD, thermal, and spectroscopic methods. Yield, physical stability, and dissolution profiles are also assessed.**

***Results:*** **The properties of the polymer greatly influenced the ability to produce glass solutions. With decreases in $T_g$ and hydrophilicity, melt extrusion became the more viable of the two preparative techniques. Although glass solutions were successfully prepared, the greater the difference in component solubility parameter, the less physically stable the formulation.**

***Conclusion:*** **Consideration must be given to the characteristics of the polymer when selecting for glass solution formulation. Although a number of process parameters can be varied for melt extrusion and spray drying, their ability to overcome fundamental differences in the physical parameters discussed is limited.**

**Keywords** melt extrusion; spray drying; carbamazepine; dipyridamole; PVP/VA copolymer and physical stability

## INTRODUCTION

The biopharmaceutical classification system (BCS) defines compounds with dissolution rate limited bioavailability as class II (Amidon, Lennernas, Shah, & Crison, 1995). Class II compounds often require formulation approaches to obtain sufficient oral bioavailability. One formulation approach is to convert a crystalline compound to the amorphous form, thereby increasing its saturation solubility (*Cs*) and dissolution rate.

The amorphous form is thermodynamically unstable. Because of this inherent instability, a large amount of research has been carried out into amorphous stabilization approaches such as coformulation with polymers to produce glass solutions (Chokshi, Sandhu, Iyer, Shah, et al., 2005; Verreck, Six, Van den Mooter, Baert, et al., 2003). A number of excipients (e.g., PVP, sugars, and cellulose derivatives) have been used in the formulation of glass solutions (Ford, 1986; Ohara, Kitamura, Kitagawa, & Terada, 2005; Simonelli et al., 1969; Zhang & McGinty, 2000). Polymer characteristics that influence glass solution properties include hydrophilicity, solubility parameter, glass transition temperature ($T_g$), hygroscopicity, and ability to accept/donate hydrogen bonds. Of these characteristics, one of the most important, irrespective of method of manufacture, is hydrogen bonding. Beten and Moes (1994) found that two dipyridamole:Eudragit solid-dispersions had contrasting dissolution profiles when prepared with two similar yet chemically distinct Eudragit polymers. The pH dependent dissolution profile was altered when a solid-dispersion was prepared with Eudragit S (which was capable of hydrogen bonding) but not Eudragit RL (which could not hydrogen bond).

The hydrophilic excipients that have been used to prepare glass solutions are often also very hygroscopic (Buhler, 2001). As a result, polymers such as polyvinyl pyrrolidone (PVP), (which has a high enough $T_g$ to exert a significant anti-plasticizing effect and a solubility parameter value of similar value to many drug substances (165°C and 23.7 $MPa^{1/2}$ for K 30)), may have their effect diminished by water plasticizing the product. Typically, a glass solution $T_g$ of > 50°C above the storage temperature is required to provide physical stability (Yoshioka, Hancock, & Zografi, 1994).

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Polyvinyl acetate (PVA) is an amorphous polymer, which is significantly less water soluble and hygroscopic than PVP. The $T_g$ and solubility parameter values of PVA (36.5°C and 10.2 $MPa^{1/2}$) are also significantly lower than those of PVP (165°C and 23.6 $MPa^{1/2}$). The solubility parameter has an impact on the ability to form a miscible single-phase product. Class II drug substances typically have solubility parameters of between 20 and 30 $MPa^{1/2}$. If the solubility parameters are greater than 10 $mPa^{1/2}$ apart, a partially crystalline or two-phase amorphous product may result (Forster et al., 2001).

A number of studies have also looked at formulating glass solutions using a copolymer of PVP and PVA (typically at a 60:40 ratio) (Moneghini, Voinovich, Princivalle, & Magarotto, 2000; Vojnovic, Rubessa, Bogataj, & Mrhar, 1993; Zingone & Rubessa, 1994). As the ratio of PVP to PVA is decreased, copolymer hydrophilicity, hygroscopicity, solubility parameter values, and propensity to hydrogen bond will also be decreased. The purpose of this paper is therefore to investigate the influence that two different PVP/VA copolymers (PVP/VA 64 and PVP/VA 37) have on the viability of two commonly used glass solution preparative techniques; melt extrusion, and spray drying.

The two drug substances used for this study are carbamazepine and dipyridamole. A summary of the properties of these drug substances has been reported previously (Patterson, James, Forster, Lancaster, et al., 2005). Previous work has demonstrated that these compounds are thermally stable but require formulation as glass solutions to be physically stable in the amorphous form (Patterson, James, Forster, Lancaster, Butler, & Rades, 2007).

The merits of three different glass solution preparative techniques (melt extrusion, spray drying, and ball milling) have been reported previously by this group using the PVP polymer (Patterson et al., 2007). Successful glass solution preparation can be assessed on the basis of two parameters: yield and whether the product is present in form of a single amorphous phase. The relationship between formulation variables (polymer $T_g$, hygroscopicity, solubility parameter, and propensity for hydrogen bonding) and successful glass solution preparation via each preparative technique will be determined.

## MATERIALS AND METHODS

### Materials

Study compounds were characterized and used as received from the supplier (Sigma Aldrich Ltd.). All substances were of analytical grade. Polymers were characterized and used as received (PVP K 30, GlaxoSmithKline and PVP/VA 64, BASF) except for PVP/VA 37 (BASF), which was precipitated from a solution by rotary evaporation (see below).

### Preparative Methods

*Spray Drying*

Drug:polymer mixtures (10 g) (1:2 w/w) were dissolved in 250 mL of dimethyl formamide (DMF) and spray dried using a Büchi B-191 spray-drier. The following spray drying conditions were used: 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 PVP/VA 64 products were then dried in a vacuum oven at 40°C for 24 h and then 55°C for a further 24 h. The PVP/VA 37 products were not dried post spray drying.

*Melt Extrusion*

Drug and polymer mixtures (300 g) (1:2 w/w) were physically mixed in a plastic bag for 5 min. The resultant physical blend was then extruded using a Brabender Plasticorder PL2000 twin-screw melt extruder (diameter 3¼ inch, L/D ratio 18) (Duisburg, Germany). The extruder was composed of four heating zones. The 'throat' was maintained at a temperature between 80–100°C. The temperatures at which the three other zones were maintained were compound dependent. Carbamazepine; zone 1: 188°C, zone 2: 185°C and zone 3: 185°C. Dipyridamole; 167, 162, and 162°C. All products were extruded at approximately 10 RPM.

*Rotary Evaporation of PVP/VA 37 Copolymer*

PVP/VA 37 was obtained from BASF as a 50% w/v solution in isopropanol. A Büchi rotary evaporator was used to remove the solvent (heating bath B490, vacuum controller V-800 and Rotavapour R-205). Approximately 300 g of polymer solution was added to a 2 L Büchi flask, and was then rotary evaporated for 2 h at 60°C, at a speed of 100 RPM and under reduced pressure (20 mbar). The product was then mechanically removed and placed under vacuum in an oven at ambient temperature for 48 h.

### Analytical Methods

*Fourier Transform Infrared Spectroscopy (FT-IR)*

Samples were analyzed using an attenuated total reflectance (ATR) germanium crystal accessory (Avatar 360 FT-IR model 360, Thermo Nicolet). The instrument was calibrated using polystyrene and spectra were recorded from 4000–700 $cm^{-1}$ using 64 sample / background scans and 4.0 $cm^{-1}$ resolution. All samples were measured in duplicate and data was analyzed using Omnic E.S.P. v5.1 software.

*Polarized Light Microscopy (PLM)*

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

*Modulated Temperature Differential Scanning Calorimetry (MTDSC)*

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 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 to ensure separation of the reversing and nonreversing components; carbamazepine: ± 0.42°C/80 sec at 2°C/min; dipyridamole: ± 0.53°C/40 sec at 5°C/min. All measurements were carried out in duplicate and results analyzed using Universal Analysis 2000 software.

*Thermogravimetric Analysis (TGA)*

A TA Instruments Hi-Res TGA 2950 Thermogravimetric Analyzer was used. This equipment was calibrated for weight using a 100 mg weight (Mettler, Toledo) and temperature using 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 aluminium pans (Perkin Elmer) to 200°C. Data was collected and analyzed using Universal Analysis software v3.0 (TA Instruments).

*X-Ray Powder Diffractometry (XRPD)*

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

*Gravimetric Vapor Sorption (GVS)*

A Hiden Analytical Moisture Sorption Analyzer model IGA Sorp was used. The machine was calibrated for weight with a 100 mg weight (Gotti, Kern, and Sohn GmbH, Germany) and relative humidity using saturated salt solutions. Samples (40–60 mg) were analyzed using stainless steel mesh baskets. Each sample underwent isothermal analysis at 25°C. The initial step was adsorption from 30 to 90% RH followed by desorption to 10% RH and finally adsorption back to 30% RH, all in 10% RH steps. The minimum time for each step was 15 min; the maximum was 180 min with equilibrium weight change measured using the Hiden software.

*Dissolution*

Dissolution testing was carried out under sink conditions using a VanKel USP II dissolution apparatus (fluid pump Model 17–2300, water bath VK750D, water bath stirrer VK7010). Sample powders were pre-wet with media and added to the dissolution vessel. Dissolution testing was carried out at 37.5 ±0.5°C (Digitron Type K thermocouple thermometer). Solubility values for drug in media were determined and the amount of drug added to solution was equivalent to 10–30% of the solubility value determined. Vessels were stirred at 50 RPM. Samples underwent online UV analysis (Hewlett Packard 8453) at time points 0, 2, 5, 10, 15, 20, 30, 45, and 60 min. Samples were filtered with a 10 μm filters (Anachem). The dissolution media used was pH 6.8 0.1M phosphate buffer[1], degassed prior to commencement of the dissolution run (Copley Dissofill, model DSF2). Standard curves were prepared by dissolving drug in acetonitrile:water (1:1) (carbamazepine) or acetonitrile:pH 6.8 buffer (1:1) (dipyridamole). Drug concentration, media, and wavelength of detection were all compound specific (carbamazepine: 50 mg / 900 mL, 278–282 nm, and dipyridamole: 6 mg / 500 mL, 288–292 nm). All analysis was carried out in triplicate.

*Physical Stability*

Products were placed on physical stability for 1 week (25°C / 75% RH and 40°C / < 10% RH) and 8 weeks (25°C/75% RH and 40°C/< 10% RH). Approximately 300 mg of sample was placed in an open 20 mL scintillation vial. The 25°C / 75% RH samples were stored in the 25°C / 75% RH controlled temperature and humidity environmental stability room at GlaxoSmithKline, Ware. The 40°C / <10% RH samples were stored over silica gel in sealed desiccators in a 40°C / 20% RH stability room.

## RESULTS AND DISCUSSION

### Copolymer Characterization

XRPD showed that PVP/VA 64 was amorphous and DSC confirmed that it was a single-phase amorphous product with a $T_g$ of 106°C (Figure 1). The FT-IR spectrum of PVP/VA 64 is shown in Figure 2. The copolymer has two regions of interest for potential drug interactions: the vinyl pyrrolidone monomer carbonyl moiety band in the 1670 $cm^{-1}$ region and the vinyl acetate monomer carbonyl moiety band in the 1730 $cm^{-1}$. Both of these moieties could theoretically accept a hydrogen group.

XRPD analysis also confirmed that the PVP/VA 37 copolymer was amorphous. DSC analysis confirmed a single-phase amorphous product with a $T_g$ of 55°C (Figure 1). The FT-IR spectrum of PVP/VA 37 is shown in Figure 2. The vinyl acetate carbonyl band (1732 $cm^{-1}$) is increased in intensity compared to PVP/VA 64 with the increased proportion of PVA. The $T_g$ of the copolymer has decreased as the proportion of PVA is increased. This is an expected finding based on the respective $T_g$s of the two components of the copolymer (Figure 1). TGA analysis showed a solvent content of 2% (w/w). This was deemed acceptable, as the complete removal of residual isopropanol was difficult without heating the polymer above the $T_g$.

[1]pH 6.8 buffer: 20 L prepared by addition of 10 L of $Na_2HPO_4.2H_2O$ 17.8 g/L to 10 L of $NaH_2PO_4.H_2O$ 13.8 g/L. pH was confirmed using a pH meter.

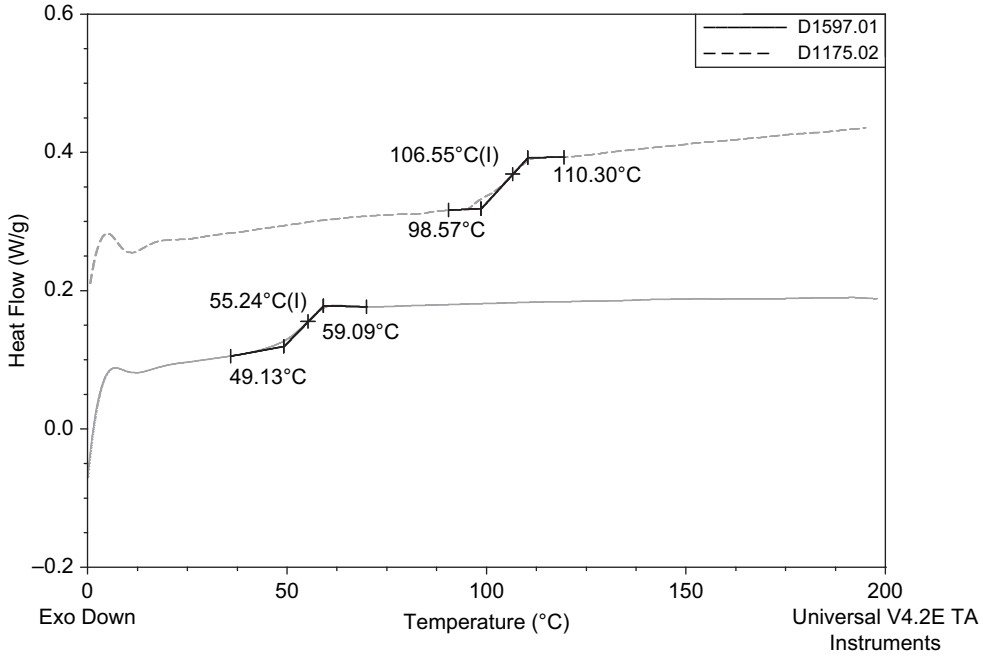


FIGURE 1. DSC of (top to bottom) PVP/VA 64 and PVP/VA 37.

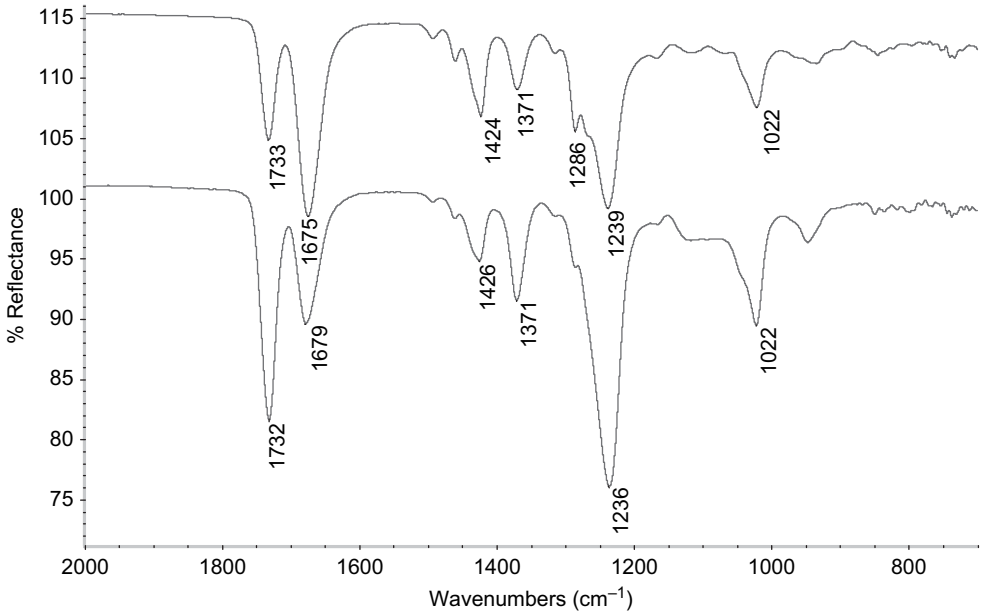


FIGURE 2. FT-IR of (top to bottom) PVP/VA 64 and PVP/VA 37.

The solubility parameter values for the various components are listed in Table 1. The copolymer solubility parameter value moves further away from those of the study compounds as the PVA content is increased. The respective copolymer solubility parameter values have been determined by direct addition of their respective values multiplied by the proportion present (Table 1). This provides a useful 'average solubility parameter value' as a guide, however it must be remembered that PVP/VA is a copolymer, and there might be PVP and PVA rich regions.

## Melt Extrusion

Copolymer selection (and subsequent changes in product $T_g$) had a large effect on the melt extrusion process. Previous

TABLE 1
Solubility Parameter Values

| Compound | D (Hildebrand) ($MPa^{1/2}$) |
|---|---|
| Carbamazepine | 24.8 |
| Dipyridamole | 29.6 |
| PVP K 30 | 23.7 |
| PVA | 10.2 |
| PVP/VA 64 | 18.3* |
| PVP/VA 37 | 14.3* |

*Values based on addition of values for each component.

investigations into extrusion of PVP K 30 products at this drug:polymer ratio showed that the high viscosity of the polymer made the extrusion process difficult (Patterson et al., 2007). To overcome this, it was necessary to extrude at a high temperature (10°C above drug melting point) and relatively low RPM (6–8 RPM). When carbamazepine (CBZ) and dipyridamole (DPM) were extruded with the PVP/VA 64 and PVP/VA 37 copolymers under these conditions, the products were less viscous and easy to extrude.

The PVP/VA 64 copolymer products were sufficiently molten under these extrusion conditions to operate at a higher RPM (10–12 RPM). The PVP/VA 37 extrudates produced were thin, low viscosity strands. This low viscosity limited the RPM at which extrusion could be carried out as at the elevated RPM the final product was almost liquefied. This low viscosity could not be compensated for by decreasing the extrusion temperature, as this could have resulted in residual API content.

XRPD and MTDSC analysis of the extrudates showed that all had formed single-phase amorphous products (Table 2 and Figure 3).

TABLE 2
XRPD and PLM of CBZ 64/37 ME, SD Products and DPM 64/37 ME, SD Products

| Products | XRPD | PLM |
|---|---|---|
| CBZ:PVP/VA 64 ME | A | A/C |
| CBZ:PVP/VA 64 SD | A | A/C |
| CBZ:PVP/VA 37 ME | A | A/C |
| CBZ:PVP/VA 37 SD | A | A/C |
| DPM:PVP/VA 64 ME | A | A/A/C |
| DPM:PVP/VA 64 SD | A | A |
| DPM:PVP/VA 37 ME | A | A |
| DPM:PVP/VA 37 SD | A | A |

C = crystalline, A = amorphous, A/C = amorphous with small regions of crystallinity, A/A/C = predominantly amorphous with small regions of birefringence.

The main consideration when processing the CBZ:PVP/VA 37 product was the impact of the decreased viscosity. While the PVP/VA 64 product viscosity was suitable for processing at 10°C greater than the drug melting point, the PVP/VA 37 extrudate was almost liquefied as it left the extruder; this limited the practicability of extruding this copolymer with drugs with high melting points (>120°C). MTDSC analysis of the CBZ:PVP/VA 37 product showed a $T_g$ of 38°C, which is a negative deviation from the value predicted by the Gordon Taylor equation (Figures 3 and 4) (Gordon & Taylor, 1952). This negative deviation is most likely a result of plasticization by water. With such a low temperature $T_g$, any residual water present in the sample will not have evaporated to the extent observed with PVP/VA 64 products. Cyclic DSC analysis resulted in an increase in $T_g$ to 53°C. This result confirmed the influence that absorbed water or residual solvent can have on product $T_g$ and illustrates why hygroscopicity and storage conditions must be considered. The amorphous stability of CBZ:PVP/VA 37 extrudate was lower than the PVP/VA 64 product, during DSC analysis a recrystallization exotherm followed by a melt endotherm was observed[2].

Similarly to the carbamazepine products, good yields were obtained with DPM:PVP/VA 64. Analysis showed that the DPM:PVP/VA 64 melt extrudate was amorphous (Table 2). The $T_g$ value of 91°C is significantly higher than that calculated with the Gordon Taylor equation (81°C). FT-IR analysis indicated that the carbonyl group of the PVP monomer had undergone some conjugation compared to neat PVP/VA 64 as there was a decrease in band wavenumber. However this could not be directly attributed to dipyridamole. The influence that dipyridamole had on PVP monomer carbonyl conjugation was qualitatively investigated previously by our group (Patterson et al., 2007). The moisture content was determined (2.38% w/w) and then corrected for drug:polymer ratio present (2.38% / 0.66 = 3.60% water content to PVP/VA 64). Given that PVA is not hygroscopic and no interaction between water and PVA was observed by FT-IR, adjusted water content of 6.0% was calculated for the PVP part of the polymer component (3.60% / 0.60 = 6.01% water content). On the basis of this assumption, a PVP carbonyl wavenumber of 1664 $cm^{-1}$ was predicted which was in good agreement with the experimental value (1663 $cm^{-1}$). This indicates that the extent of interaction between dipyridamole and the PVP monomer was not as large as that observed in the DPM:PVP products (Patterson et al., 2007). This decreased interaction is most likely due to steric hindrance of the PVA monomer. No evidence of conjugation was observed for the PVA carbonyl group. Dipyridamole has four potential sites per molecule from which it can donate hydrogen bonds to the PVP carbonyl of the copolymer. The vinyl acetate carbonyl moiety of the PVA is not as electronegative as the

[2]During cyclic DSC analysis the maximum temperature of 100 °C was significantly lower than the temperature at which an onset of recrystallisation was observed.

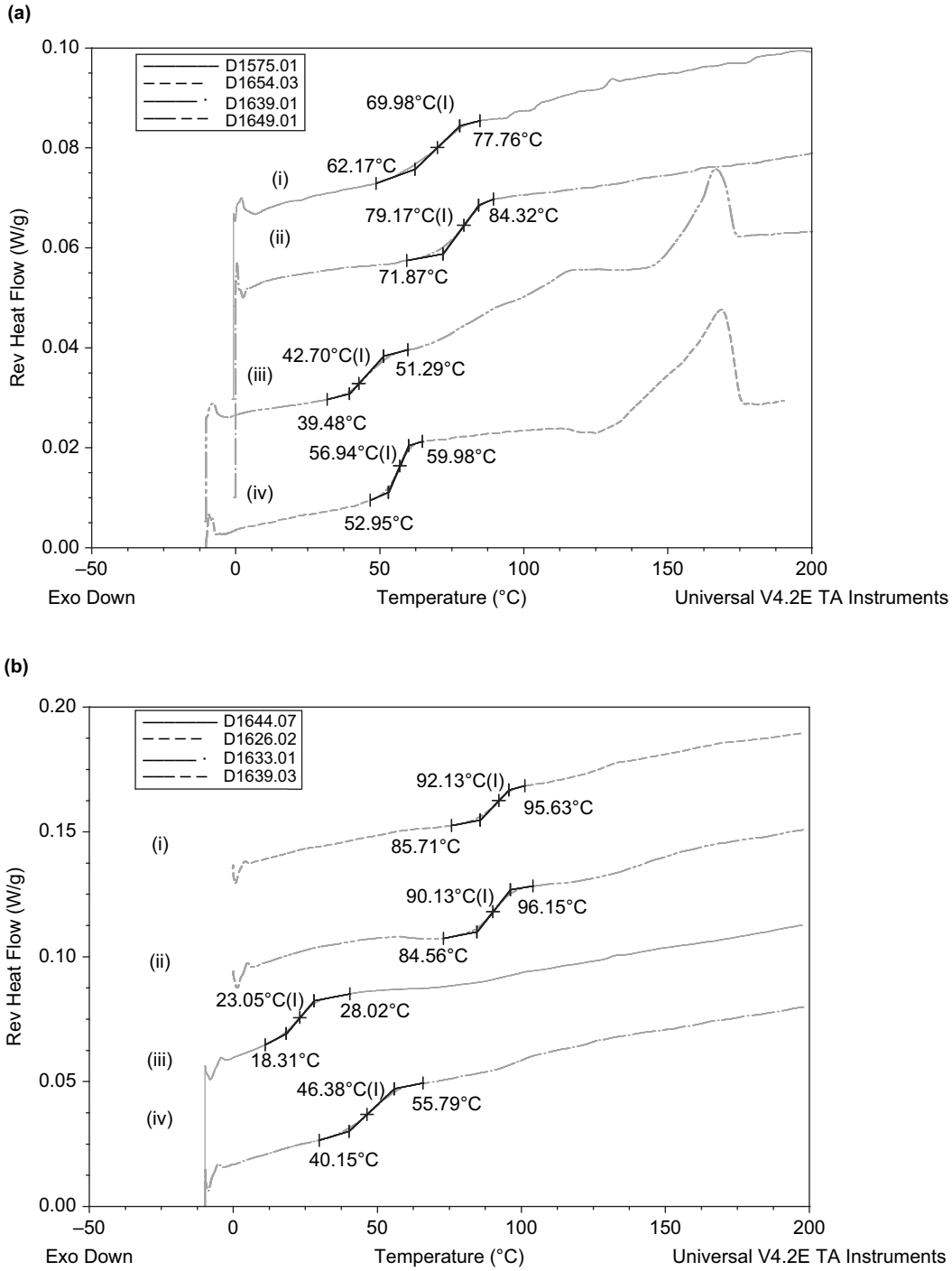


FIGURE 3. MTDSC of (a) (i) CBZ:PVP/VA 64 melt extrudate and (ii) spray-dried products, (iii) CBZ:PVP/VA 37 melt extrudate and (iv) spray-dried products, (b) (i) DPM:PVP/VA 64 melt extrudate and (ii) spray-dried products and (iii) DPM:PVP/VA 37 melt extrudate and (iv) spray-dried products.

PVP carbonyl group, and as stated previously, no evidence of a DPM:PVA interaction has been observed by FT-IR.

As with the CBZ:PVP/VA 37 extrudate, the DPM:PVP/VA 37 product was amorphous (Table 2), however the key consideration again was the low product viscosity. In spite of the large difference in solubility parameter for this copolymer and dipyridamole (Table 1), MTDSC analysis showed a single-phase amorphous product (Figure 3). The $T_g$ of the product was variable, ranging from 23 to 35°C, which is likely a result of water plasticizing the sample. Similarly to the CBZ:PVP/VA 37 product, preheating the sample resulted in an increase in $T_g$ from 38 to 45°C.

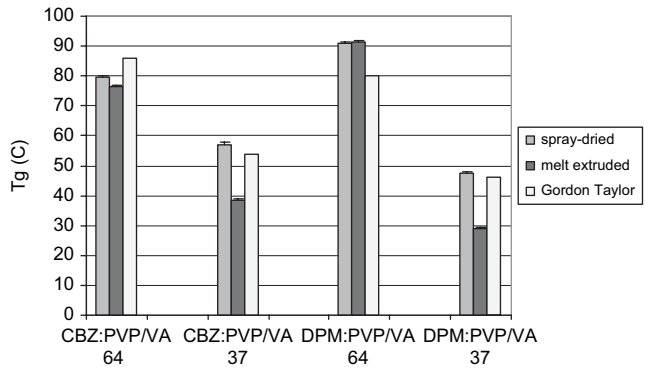


FIGURE 4. Influence of preparative technique on deviation in product $T_g$ values from those predicted using the Gordon Taylor equation.

## Spray Drying

MTDSC analysis of the CBZ:PVP/VA 64 spray dried product showed a single phase amorphous system with a single $T_g$ at 79°C. This value is lower than that predicted by the Gordon Taylor equation (86°C). While XRPD confirmed that the product was amorphous, PLM did show some small regions of birefringence after the post spray drying solvent removal step.

Spray drying carbamazepine with PVP/VA 37 resulted in an unacceptably low yield of 2.4% w/w. The product adhered to the walls of the spray drier and had to be manually removed. However unlike the PVP/VA 64 product (which also had to be manually removed from the cyclone), the product was extremely rubbery in nature. This is most likely a result of the outlet temperature being greater than the product $T_g$ (Figure 5) and demonstrates the influence of $T_g$ on the selection of the glass solution preparative process.

XRPD showed that while the product was rubbery, it remained predominantly amorphous (Krahn & Mielck, 1987). FT-IR of the PVP/VA 37 product showed a weak and broad N-H band at 3480 $cm^{-1}$, and the shape of the alkene bands

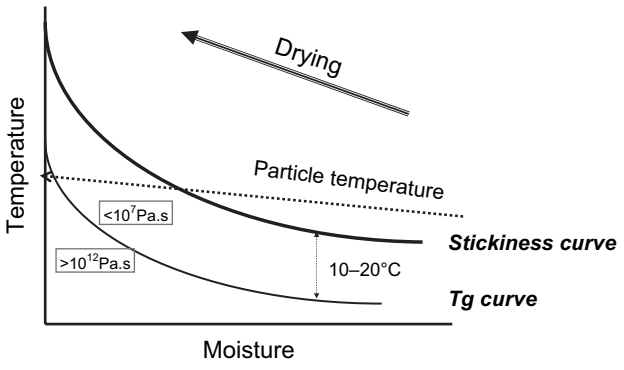


FIGURE 5. Stickiness and glass transition curves during spray-drying (modified from Bhandari, 2004).

(ca. 1600 $cm^{-1}$) indicated that the product was amorphous (Krahn & Mielck, 1987). No variation was observed in the wavenumber of the vinyl acetate and vinyl pyrrolidone carbonyl bands, which remained at 1732 and 1670 $cm^{-1}$, respectively. However PLM analysis also indicated small regions of birefringence. MTDSC analysis showed a recrystallization exotherm in the nonreversing heat flow, followed by a melt endotherm at 167°C (Figure 3). The presence of this recrystallization exotherm during analysis indicates that the glass solution was less stable than the other glass solutions prepared. Because of the recrystallization exotherm during heating, DSC analysis could not conclusively determine whether there was low-level crystalline content prior to heating. The decreased stability is likely a result of the lack of hydrogen bonding and the increased difference in solubility parameter values (Table 1).

Spray drying of dipyridamole with PVP/VA 64 resulted in an amorphous product (Table 2). TGA showed that the solvent content was significantly lower than for a PVP product of the same ratio (Patterson et al., 2007). This is likely to be due to the low polymer hygroscopicity of PVP/VA 64.

MTDSC analysis confirmed the amorphous nature of the product and showed that the components were completely miscible with a single $T_g$ at 91°C. As seen previously with the DPM:PVP products (Patterson et al., 2007), the experimentally determined $T_g$ was higher than that predicted by the Gordon Taylor equation (80°C) (Figure 4). This is likely to be a result of hydrogen bonding between dipyridamole and PVP in the copolymer.

Analysis of the DPM:PVP/VA 37 product showed that it was amorphous (Table 2). However, as seen with the CBZ:PVP/VA 37 product, the process resulted in an unacceptably low yield of 2.4% w/w. This was a result of the outlet temperature (74°C) being greater than the product $T_g$ (48°C).

Unlike the CBZ:PVP/VA 37 product, no recrystallization exotherm was observed during MTDSC analysis of the DPM:PVP/VA 37 product. The reversing heat flow analysis did however indicate that the product had two $T_g$'s (48 and 100°C), this indicates that a single-phase product had not been formed (Figure 3). The temperature at which the second $T_g$ occurred was unexpectedly high given the dipyridamole and PVP/VA 37 $T_g$ values of 40 and 56°C. The PVP/VA 37 copolymer used was a random copolymer and will therefore have PVP rich regions. This may explain the second $T_g$ at 100°C. With at least some of the PVP present as a separate phase, the anti-plasticizing effect of PVP/VA 37 would be diminished.

Spray dried product characterization showed a number of polymer specific characteristics. As the ratio of PVP to PVA was decreased, residual solvent content and yields were also decreased. These results indicated that when the product or polymer has a low $T_g$, spray drying is an inappropriate preparative technique if outlet temperature cannot be kept lower than the product $T_g$. This may be overcome to a limited extent by selection of a more volatile solvent.

An indication of the hydrogen bonding behavior of drug:copolymer systems may be obtained for PVP/VA 64 products by studying the deviation between experimentally derived $T_g$ and that of the Gordon Taylor equation. However, analysis of the influence of hydrogen bonding on $T_g$ deviation for PVP/VA 37 products is of limited use as residual moisture plasticizes the samples.

## Physical Stability

FT-IR and MTDSC were used to analyze physical stability samples, to determine recrystallization behavior and whether they remained as one phase amorphous systems respectively. Differences in the FT-IR spectrum associated with the amorphous and crystalline form(s) of carbamazepine and dipyridamole have been established in previous work (Patterson et al., 2005). XRPD analysis of high RH physical stability samples was only used to confirm findings, as this technique becomes difficult to use with product agglomeration during storage (Patterson et al., 2007).

### *Analysis of Spray Dried Carbamazepine Stability Samples*

Storage of CBZ:PVP/VA 64 products (spray dried and melt extruded) for 8 weeks at low humidity did not result in any recrystallization (Table 3). However, the high humidity CBZ:PVP/VA 64 spray-dried product exhibited an N-H stretch at 3480 $cm^{-1}$ and a shoulder at 3465 $cm^{-1}$, the presence and relative intensity of these two bands indicates that recrystallization predominantly to form I had occurred (Krahn & Mielck, 1987), but that there had also been some form III formation. The bands in the 1600 $cm^{-1}$ region confirmed these findings. No bands associated with carbamazepine dihydrate formation were observed.

Thermal analysis of the CBZ:PVP/VA 64 spray-dried product confirmed that low humidity storage did not result in any recrystallization after 8 weeks. The only changes observed after low RH storage were larger relaxation enthalpies associated with the $T_g$. After storage at high humidity however, two $T_g$s were observed, the first was consistent with an amorphous carbamazepine region (48°C) and the second with a CBZ:PVP/VA 64 'glass solution' phase (99°C). The 'glass solution' $T_g$ was higher than that immediately post preparation (80°C). A melt endotherm was also observed indicating that there had been some recrystallization during storage (Figure 6). Therefore the increase in 'glass solution' $T_g$ is likely a result of the carbamazepine recrystallization, and also the phase separation.

### *Analysis of Spray Dried Dipyridamole Stability Samples*

There are a number of bands in the dipyridamole FT-IR spectrum that allow crystalline content determination, these include the asymmetric C-H stretch band (ca. 2850 $cm^{-1}$) and the $CH_2$ bending bands (ca. 1450 $cm^{-1}$) (Kuhnert-Brandstatter & Wurian, 1982; Patterson et al., 2005). FT-IR analysis of the DPM:PVP/VA 64 spray-dried products stored at low humidity showed that they did not recrystallize. The high humidity samples however showed bands at 1440 $cm^{-1}$ and at 2858 $cm^{-1}$ that indicated some recrystallization had occurred (Table 3).

Thermal analysis of 8 week stability samples showed that the DPM:PVP/VA 64 spray-dried products stored under dry conditions had not undergone any physical change, while the products stored at high humidity now exhibited two $T_g$s; one lower than that of the product post preparation and one at a similar temperature to that observed post spray drying (Figure 3). This difference in $T_g$ indicates that some regions may have absorbed water and some have not. This may indicate a surface mediated effect, i.e. the spray dried product may have adsorbed water on the surface and is subsequently plasticized. However, away from the particle surface the bulk product remains unplasticized.

The physical stability of the spray dried PVP/VA 37 products could not be determined due to the very low yields.

### *Analysis of Melt Extruded Carbamazepine Stability Samples*

The CBZ:PVP/VA 64 extrudate remained amorphous when stored at low humidity, however at high humidity it recrystallized to form III. MTDSC analysis showed an increase in the

TABLE 3
Summary of Water Content (% w/w, Analyzed by TGA) and Physical Stability of Drug:Polymer Products Prepared by Different Preparative Techniques (Analyzed by FT-IR) After 8 Weeks Storage

| Drug | Polymer | Preparative Technique | 25°C / 75% RH | | 40°C / 10% RH | |
|---|---|---|---|---|---|---|
| | | | FT-IR | TGA | FT-IR | TGA |
| Carbamazepine | PVP/VA 64 | SD | C | 4.5 | A | 2.0 |
| | | ME | C | 6.8 | A | 2.1 |
| Carbamazepine | PVP/VA 37 | ME | C | 1.9 | A | 1.4 |
| Dipyridamole | PVP/VA 64 | SD | C | 6.0 | A | 0.4 |
| | | ME | C | 6.0 | A | 2.2 |
| Dipyridamole | PVP/VA 37 | ME | A/C | 1.8 | A | 1.4 |

A = amorphous, C = crystalline, A/C = partially crystalline, SD = spray-dried and ME = melt extruded.

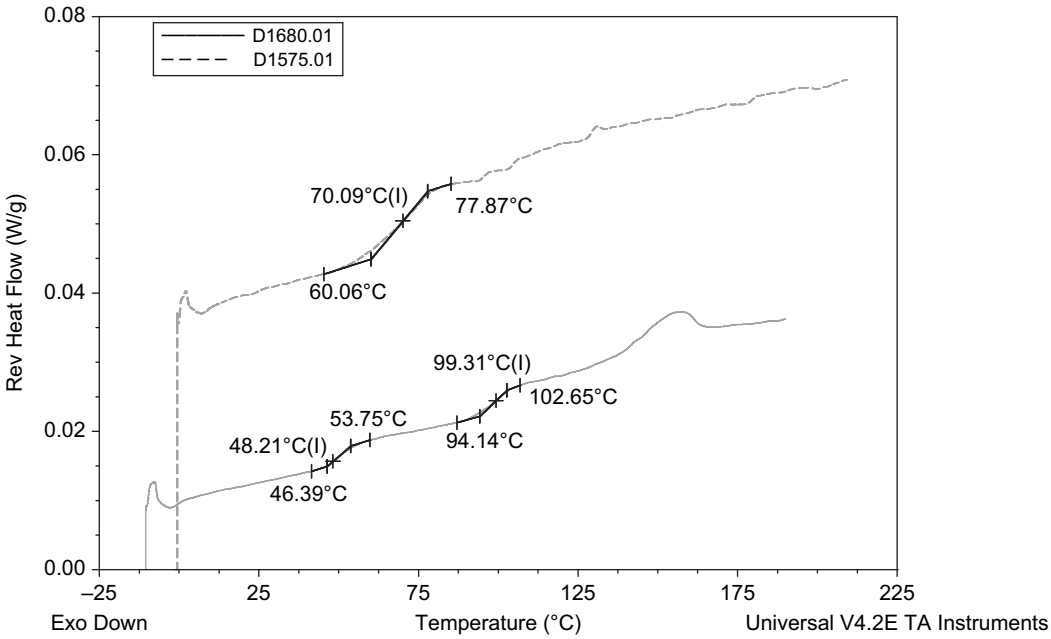


FIGURE 6. MTDSC of (top to bottom) CBZ:PVP/VA 64 glass solution spray-dried immediately post preparation and after 8 weeks storage at 25°C/75% RH.

product $T_g$; this can be attributed to a decrease in plasticization as a result of carbamazepine recrystallization (Patterson, James, Forster, & Rades, 2003). However, unlike the spray dried CBZ:PVP/VA 64 product, only one $T_g$ was observed and this was consistent with a glass solution (76°C). No separation of a single CBZ amorphous phase was observed after storage at elevated RH.

XRPD, PLM, and FT-IR indicated that the CBZ:PVP/VA 37 extrudate also remained amorphous when stored at low humidity (Table 2). However FT-IR analysis of samples stored at high humidity showed evidence of recrystallization. The sample had an intense N-H stretch at 3465 $cm^{-1}$ indicative of form III and a weaker stretch at 3485 $cm^{-1}$ indicating the presence of some form I. Unlike the PVP/VA 64 product, the RH at which the sample was stored did not influence the water content with 1.9% at 25°C / 75% RH and 1.4% at 40°C / 10% RH. MTDSC analysis showed a slight increase in the product $T_g$ after it had been stored at high humidity. However, carbamazepine and PVP/VA 37 have similar $T_g$s (56 and 55°C, respectively) and therefore recrystallization of the drug may not result in significant changes in glass solution $T_g$. The lower product $T_g$ also means that any moisture absorbed is likely to have an increased plasticization effect; as unlike the higher $T_g$ PVP/VA 64 products, evaporation during thermal analysis will not have begun prior to $T_g$ onset.

*Analysis of Melt Extruded Dipyridamole Stability Samples*

XRPD, PLM, and FT-IR indicated that the DPM:PVP/VA 64 extrudate also remained amorphous when stored at low humidity (Table 2). FT-IR analysis of samples stored at high humidity showed a band present at 1440 $cm^{-1}$, the presence of which had been identified as an indicator of crystallinity in a previous study (Patterson et al., 2005). The presence of this band therefore indicates that some recrystallization has occurred. XRPD analysis of the dipyridamole stability samples was limited to those samples stored at low humidity. This was because of the product coarsening into large agglomerates when stored at high RH. MTDSC analysis of the samples stored under dry conditions showed that they remained as single-phase amorphous products. When the samples were stored at high humidity, the $T_g$ of the glass solution decreased from 92 to 51°C (Figure 3). This decrease in $T_g$ occurred even though there had been partial dipyridamole recrystallization (as shown by FT-IR analysis). When carbamazepine had recrystallized from the CBZ:PVP/VA 64 glass solution, it resulted in an increase in $T_g$ towards that of the copolymer. The observed plasticization of the DPM:PVP/VA 64 product, in spite of the observed recrystallization is likely to be a result of increased moisture absorption, this may also explain the observed product coarsening. TGA showed that the product stored at high RH had 6.0% moisture content, while the CBZ:PVP/VA 64 extrudate had a similar value of 6.8%. Although the two products have similar moisture content, the observed behavior as a result of high RH storage was very different. This may be due to differences in affinity for water between the two drug substances, and hence the distribution of water in the glass solution.

XRPD, PLM, and FT-IR indicated that the DPM:PVP/VA 37 extrudate also remained amorphous when stored at low humidity (Table 3). FT-IR analysis of samples stored at high

humidity showed a band present at 1440 $cm^{-1}$, indicating some recrystallization. Irrespective of storage RH, the DPM:PVP/VA 37 product absorbed a comparatively small amount of moisture (Table 3). MTDSC analysis showed no change in extrudate $T_g$ after storage under dry conditions (Figure 3). After storage at high RH, the $T_g$ had increased from 35 to 54°C. This behavior differs from that observed with the DPM:PVP/VA 64 extrudate which had a decreased $T_g$. The increase in $T_g$ may be a result of recrystallization of dipyridamole and its subsequent decreased plasticizing effect and also the decreased hygroscopicity of the PVP/VA 37 copolymer.

## Dissolution

*Carbamazepine Products Dissolution*

The dissolution behavior (Q10 and Q60) of the carbamazepine physical blends and spray dried and melt extruded products are shown (Table 4). The CBZ:PVP/VA 64 glass solutions showed an increased rate of dissolution compared to the physical blend. Of the two glass solution preparative techniques, melt extrusion showed the higher improvement. Spray-drying resulted in a minor improvement, however compared to that of the physical blend, it would not be considered enough to justify conversion to the amorphous form. The difference in performance between the two techniques was most pronounced at the Q10 time point. Glass solution preparation with the PVP/VA 37 copolymer resulted in retardation of the dissolution rate. The degree of retardation was greater for the melt extrudate than for the physical blend. This is most likely because of the decreased hydrophilicity of the single-phase amorphous product, there is less significantly less intimacy when a physical blend.

*Dipyridamole Products Dissolution*

The DPM:PVP/VA 64 glass solutions showed a similar relationship between preparative technique and dissolution rate to that seen for the CBZ:PVP/VA 64 products. The greatest improvement in dissolution rate was observed with the melt extrudate, and this was most pronounced after 10 min. The spray-dried product showed an initial improvement in dissolution rate, however this then plateaued and after 60 min was less than that of the physical blend. When formulated as glass solutions, the PVP/VA 37 products did not show the clear decrease in dissolution rate compared to the physical blend. The extrudate had a similar dissolution rate to the physical blend while the spray dried product showed a greater rate of dissolution. The variability of the spray dried product was however much greater.

The hydrophilicity of the polymer was shown to influence the dissolution rate of the products (Table 4). Spray dried and melt extruded PVP/VA 64 products had increased dissolution rates, however not to the extent observed with spray-dried and melt extruded PVP products (Patterson et al., 2007). Formulation with PVP/VA 37 resulted in decreased dissolution rates for most products. This is likely a result of the decreased hydrophilic nature of the copolymer with increased PVA content.

In general, the melt extrudates show a greater improvement in dissolution rate than the spray-dried products, particularly over the first 10 min.

## CONCLUSIONS

The products in this study were manufactured using only one set of melt extrusion and spray drying conditions. It is

TABLE 4
Influence of Preparative Technique and Copolymer on Dissolution of Study Compounds

| | | Dissolution % (*SD*) | | Relative Dissolution | |
|---|---|---|---|---|---|
| Drug | Product | Q10 | Q60 | Q10 | Q60 |
| Carbamazepine | Crystalline drug | 44.3 (13.5) | 58.9 (12.5) | 1.00 | 1.00 |
| | PVP/VA 64 physical blend | 52.5 (6.3) | 74.8 (15.5) | 1.18 | 1.27 |
| | PVP/VA 64 spray-dried | 55.2 (0.3) | 84.0 (1.9) | 1.25 | 1.43 |
| | PVP/VA 64 extrudate | 86.3 (12.4) | 98.8 (9.0) | 1.95 | 1.68 |
| | PVP/VA 37 physical blend | 15.3 (4.4) | 25.4 (8.4) | 0.34 | 0.43 |
| | PVP/VA 37 extrudate | 3.6 (0.7) | 8.7 (1.5) | 0.08 | 0.15 |
| Dipyridamole | Crystalline drug | 15.7 (5.7) | 19.0 (3.6) | 1.00 | 1.00 |
| | PVP/VA 64 physical blend | 31.2 (1.4) | 59.3 (6.5) | 1.99 | 3.12 |
| | PVP/VA 64 spray-dried | 44.0 (1.3) | 48.0 (2.8) | 2.80 | 2.53 |
| | PVP/VA 64 extrudate | 76.9 (4.2) | 77.5 (4.2) | 4.90 | 4.09 |
| | PVP/VA 37 physical blend | 11.4 (1.3) | 33.5 (7.0) | 0.73 | 1.77 |
| | PVP/VA 37 spray-dried | 36.1 (7.5) | 52.1 (21.0) | 2.30 | 2.74 |
| | PVP/VA 37 extrudate | 26.8 (1.5) | 30.3 (1.4) | 1.71 | 1.59 |

accepted that a number of processing parameters for melt extrusion and spray drying can be varied. However, given the importance of formulation parameters such as solubility parameter, $T_g$, hydrogen bonding, it is unlikely that the process parameters could be varied to the extent that the formulation limitations identified could be overcome.

The viability of melt extrusion depends on the ability to form a one-phase glass solution. There are processing limitations for extruding in terms of temperature (too high-potential for degradation of drug and/or polymer, too low residual drug crystallinity). Therefore there is a limited window in which process parameters can be varied to optimize a formulation.

Polymer selection while spray drying has been shown to influence the residual solvent content and extent of drug:polymer interaction and yield. For spray drying, selection of solvent and spray drying conditions will only have a limited effect as long as reasonable steps are taken to minimize residual solvent content, and the operating temperature is high enough to ensure an amorphous product. There have been previous studies that have assessed the influence of solvent polarity on the degree of hydrogen bonding in glass solutions (Najib, Suleiman, & Malakh, 1986), however the impact of this on subsequent stability has not been demonstrated. The process variable most likely to exert an effect is the lowering of the outlet temperature by using a more volatile solvent.

This study has also indicated that polymer threshold $T_g$ values (and subsequent viscosity at processing temperature) exist, below which the effectiveness of melt extrusion and spray drying is limited. FT-IR analysis showed that the extent of the drug:polymer interaction was both compound specific and related to the amount of PVP in the product. Investigation into the extent of chemical interactions between drug and copolymer indicated that dipyridamole hydrogen bonded with the carbonyl group of PVP while carbamazepine did not. This correlated with the physical stability findings, which showed that carbamazepine was more prone to recrystallization than dipyridamole. As well as hydrogen bonding, the solubility parameter values of components have been demonstrated to be key considerations when preparing glass solutions. In spite of the lack of hydrogen bonding, the similarities in solubility parameter values meant that a CBZ:PVP/VA 64 amorphous product could at least be initially formed. However, characterization of the CBZ:PVP/VA 37 products show how difficult preparation can be when both these conditions are not satisfied.

The viability of the systems is therefore essentially based on three parameters- $T_g$, solubility parameter and hydrogen bonding. We are able to assess these because of the propensity of recrystallization of the model drug substances selected. The greater the difference in solubility parameter between polymer and API, the greater the energy will have to be imparted by the process to overcome this. As a result, it appears that any PVP content below 60:40, the less viable the formulation, irrespective of the method of manufacture.

Based on this work, the ideal properties of polymer for glass solution preparation can be surmised as—suitable $T_g$ for processing, solubility parameter < 7 $MPa^{1/2}$ from that of the API, low hygroscopicity and capability of hydrogen bonding. Where formation of a glass solution is indicated, melt extrusion does have benefits over spray drying in terms of increased yield, absence of residual solvent, environmental impact, and cost.

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