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Characterization of glass solutions of poorly water-soluble drugs produced by melt extrusion with hydrophilic amorphous polymers

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Abstract

Indomethacin, lacidipine, nifedipine and tolbutamide are poorly soluble in water and may show dissolution-related low oral bioavailability. This study describes the formulation and characterization of these drugs as glass solutions with the amorphous polymers polyvinylpyrrolidone (PVP) and polyvinylpyrrolidone-co-vinyl acetate by melt extrusion. The extrudates were compared with physical mixtures of drug and polymer. X-ray powder diffraction, thermal analysis, infrared spectroscopy, scanning electron microscopy, HPLC, moisture analysis and dissolution were used to examine the physicochemical properties and chemical stability of the glass solutions prepared by melt extrusion at a 1:1 drug/polymer ratio. Depending on the temperature used, melt extrusion produced amorphous glass solutions, with markedly improved dissolution rates compared with crystalline drug. A significant physicochemical interaction between drug and polymer was found for all extrudates. This interaction was caused by hydrogen bonding (H-bonding) between the carbonyl group of the pyrrole ring of the polymer and a H-donor group of the drug. Indomethacin also showed evidence of H-bonding when physical mixtures of amorphous drug and PVP were prepared. After storage of the extrudates for 4–8 weeks at 25°C/75% relative humidity (RH) only indomethacin/polymer (1:1) extrudate remained totally amorphous. All extrudates remained amorphous when stored at 25°C/$<$ 10% RH. Differences in the physical stability of drug/polymer extrudates may be due to differences in H-bonding between the components.

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Introduction

Preparation of an amorphous solid dispersion is potentially an effective way of increasing the dissolution rate of poorly water-soluble drugs; however, few amorphous solid dispersions have been successfully marketed (Serajuddin 1999). One reason for this is likely to be the poor physical stability of formulations in the amorphous state, although several studies suggest that amorphous dispersions could be stable over the shelf-life of the product, depending on the moisture content, storage temperature and ratio of drug to polymer (Hancock & Zografi 1994; Kearney et al 1994; Yoshioka et al 1994). Other problems in the formulation of amorphous solid dispersions are the cost of preparation and the difficulty of scaling-up from laboratory formulation to production (Serajuddin 1999).

Melt extrusion is a well established preparation method in plastics technology (White et al 1987) and is currently being investigated for application in pharmaceutical dosage form development to produce drug/polymer solid dispersions (Gruenhagen 1996; Breitenbach et al 1998; Forster et al 1999; Breitenbach 2000;

Hülsmann et al 2000). During melt extrusion, drug is incorporated into polymer by melting or plasticizing both the drug and excipient using either one or two screws inside a heated barrel (Breitenbach et al 1998). The molten material is then cooled, typically on a chilled stainless steel conveyor belt. This approach may lead to formation of a solid solution of glassy amorphous drug embedded in polymer. Melt extrusion is a well controllable and scaleable process without problems associated with the use of large volumes of solvent, which limit the application of other solid dispersion manufacturing methods (Ford 1986; Serajuddin 1999). One of the most important variables in the melt extrusion process is the selection of a temperature that fully plasticizes the polymer without causing chemical decomposition of the drug.

Indomethacin, lacidipine, nifedipine and tolbutamide are poorly water-soluble drugs with dissolution-rate-limited bioavailability (Miralles et al 1982; Ali 1989; Hamza et al 1994). Both polyvinylpyrrolidone (PVP) and polyvinylpyrrolidone-co-vinyl acetate (PVP/VA) have been shown to increase solubility and dissolution of drugs when formulated as solid solutions due to a combination of a maximally decreased particle size, the amorphous state of the drug, increased wetting and increased solubility in the diffusion layer (Corrigan 1985; Shamblin & Zografi 1999). The aim of this study was to characterize melt extrudates of drug with PVP and PVP/VA, prepared over a narrow temperature range, using various physicochemical techniques.

Materials and Methods

Materials

Indomethacin (purity $> 99\%$), nifedipine (purity $> 98\%$) and tolbutamide (purity $> 99\%$) were purchased from Sigma Aldrich (Dorset, UK). Lacidipine was supplied by GlaxoWellcome (Ware, UK). PVP (k30, average MW 50 000) was obtained from GlaxoWellcome (Ware, UK). PVP/VA (60/40, MW 45000–70000) was obtained from ISP (Manchester, UK). Lacidipine and nifedipine samples were protected from light at all times. All substances were used without further purification.

Preparation of solid dispersions

Extrusion was performed in a low humidity ($< 25\%$ RH) and controlled temperature (20°C) environment using a Brabender Plasti-corder PL2000 extruder (Duisburg, Germany) with counter-rotating intermeshing twin screws. The extrusion barrel is divided into four temperature zones. For each drug/PVP blend, the first zone (throat) was initially heated by conduction from the second zone and then cooled to 20°C using a water cooler to avoid plasticized material blocking flow through the extruder. The temperature of the extrusion zones was varied to investigate the temperature range for glass solution formation. The range of temperatures used for each zone for the different drug/polymer combinations and mass ratios is shown in Table 1. The screw speed was adjusted to 20–30 rev min^{-1}, with the rate determined by output of the extruder and strain on the machine. The drug/polymer blends were manually fed into the melt extruder and the extrudates were cooled on a conveyer belt. Extrudate formed in the first 5 min of production was discarded and this step was also taken when the extrusion temperature was changed. Extrudate was stored in sealed bags with desiccant (silica gel) at less than 25°C. Indomethacin and lacidipine were extruded with PVP and PVP/VA, whereas tolbutamide and nifedipine were only extruded with PVP. Drug/polymer blends were extruded at a 1:1 mass ratio, and, additionally, indomethacin/PVP was extruded at a 4:1 mass ratio. The particle size of extrudate was reduced by milling in a Glen Creston DFH48LL hammer mill (Middlesex, UK) through a 0.5-mm screen. A particle size range of 25–250 μm was selected for analysis.

Preparation of amorphous drugs

Amorphous drug samples were prepared by melting drug in stainless steel beakers on a hotplate with a thermostat. Melts were rapidly cooled by partially submerging the beaker into ice-cold water. The resulting mass was then pulverized by light grinding in a mortar. This method of preparing the amorphous state of the drugs has been used previously to produce amorphous indomethacin and lacidipine and partially amorphous nifedipine and tolbutamide (Forster et al 1999).

Preparation of physical mixtures

Drug/polymer physical mixtures were prepared by lightly grinding accurately weighed quantities of crystalline or amorphous drug and polymer in a mortar for 2 min at the required drug/polymer level. A particle size range of 25–250 μm was selected for analysis.

X-ray powder diffraction (XRPD)

XRPD was performed on a Philips X'pert MPD with a count time of 1 s and a step size of 0.04° 2θ using Ni-filtered Cu-kα radiation (30 kV and 40 mA). Samples

Table 1 Zone temperatures of the melt extruder for drug/polymer blends (°C).

Drug	Polymer	Ratio	Run A Extruder zones[a]			Run B Extruder zones[a]			Run C Extruder zones[a]			Run D Extruder zones[a]		
			2	3	4	2	3	4	2	3	4	2	3	4
Indomethacin	PVP	1:1	165	170	170	165	165	165	150	155	160	180	180	185
	PVP	4:1	155	155	155	140	140	140	147	147	147	150	150	150
	PVP/VA	1:1	150	150	150	135	135	140	125	125	125			
Lacidipine	PVP	1:1	180	180	175	160	160	165						
	PVP/VA	1:1	170	170	170									
Nifedipine	PVP	1:1	165	165	165									
Tolbutamide	PVP	1:1	140	140	140	150	150	150	120	120	120			

[a]For each drug/polymer blend, the first zone was initially heated by conduction from the second zone and then cooled to 20°C using a water cooler to avoid plasticized material blocking flow through the machine.

were prepared as 300 mg back-filled samples. Scans with a 0.01° 2θ step size and 20 s per step were used to quantitatively assess the peak area of extrudates in an angular range characteristic for the crystalline drug (indomethacin 21.2–22.2° 2θ; lacidipine 21.5–23° 2θ; nifedipine 14.0–15.5° 2θ; tolbutamide 11.5–14.0° 2θ). Physical blends of crystalline drug in polymer were used to calibrate the XRPD on the day of use. However, it should be stated that the use of a physical mixture of amorphous and crystalline material to quantify crystallinity in a partially amorphous system may be problematic, as differences in both particle size and intimacy of mixing of the crystalline phase cannot be excluded. Peak areas were obtained using the Philips APDW software. Samples were run in duplicate and the limit of detection was approximately 1% crystalline drug.

Thermal analysis

Samples were heated in a TA Instruments 2920 DSC (Surrey, UK) at 10 K min^{-1} with a nitrogen purge at 20 mL min^{-1} using crimped aluminium pans with a pierced lid. Samples were run in duplicate and the sample size was 5–10 mg. The DSC was calibrated for baseline using empty pans, and for temperature and enthalpy using indium. The DSC was used to determine the melting points and enthalpies of samples. Modulated temperature DSC (MTDSC) was used to analyse the glass transition temperature (Tg) of the melt extrudates as the Tg was masked by an enthalpic relaxation endotherm on analysis with conventional DSC. MTDSC separates thermodynamically reversing events (such as the Tg), from non-reversing events (such as enthalpic relaxation), and its application to the analysis of the Tg has been previously described (Craig & Royall 1998). MTDSC was performed using the TA Instruments 2920 DSC with liquid nitrogen cooling accessory. Samples were sealed in aluminium pans without a vent to prevent water loss and a sample size of 5–10 mg was used. A linear heating rate of 2 K min^{-1} with an oscillation of ± 0.25 K every 40 s was applied, ensuring at least 6 modulations per thermal event. The Tg of the individual components was: indomethacin 43.7°C; lacidipine 48.0°C; nifedipine 46.7°C; tolbutamide 2.9°C; PVP 168°C; and PVP/VA 106°C.

Infrared (IR) spectroscopy

Diffuse reflectance infrared Fourier-transformed spectroscopy (DRIFTS) was performed on a Biorad FTS 175C dynamic alignment FTIR spectrophotometer using a diffuse reflectance accessory (Pike Technology, Easidiff). The powder samples were dispersed as a 5% w/w mix in KBr and scanned immediately after mixing. Mixes of drug in KBr were prepared in duplicate. Spectra involving the addition of spectra of individual components (addition spectra) were calculated using the Bio-Rad Win-IR software.

Scanning electron microscopy

Samples for analysis were coated with a thin gold–palladium layer by sputter coating (Biorad E5100, Microscience Division, Watford, UK). Coated samples were mounted onto specimen stubs with double-sided

carbon tape and were fitted into the scanning electron microscope specimen stage. The samples were investigated with a Cambridge S360 scanning electron microscope (Cambridge, UK), which was operated with an acceleration voltage of 10 kV.

Moisture analysis

Moisture content was determined by both thermogravimetry (TA Instruments 2950 analyser at a heating rate of 10 K min^{-1} and a nitrogen flow of 100 mL min^{-1}, using tared DSC pans; the instrument was calibrated for temperature using nickel and Alumel) and Karl Fischer analysis (Turbo2 blending Karl Fischer, Orion, East Sussex, UK). Moisture content was determined in duplicate for both techniques.

Chemical stability

Chemical stability was determined by HPLC. The HPLC system consisted of a HP 1090 Liquid Chromatograph (Hewlett Packard, Bracknell, UK) and an Inertsil (G L Sciences, Japan) ODS-2 column (5 μm 4.6 × 150 mm) (Phenomonex, Cheshire, UK). Online analysis was carried out at 210 nm and a drug-specific wavelength (indomethacin 318 nm; lacidipine 284 nm; nifedipine 340 nm; tolbutamide 260 nm) using a Hewlett Packard 8453 diode array spectrophotometer (Bracknell, UK) at 40°C. A sample (5 μL) of a 1 mg mL^{-1} solution of drug in acetonitrile/water (1 : 1) was injected onto the column. A gradient system of water (0.05% formic acid) and acetonitrile (0.05% formic acid) was used as mobile phase. Solutions for analysis were injected in duplicate. The chemical stability of PVP and PVP/VA at the temperatures used during extrusion was confirmed by thermogravimetry. Both polymers showed less than a 1% weight loss when heated to 200°C.

Dissolution

Dissolution was undertaken using a USP II apparatus (37°C, 50 rev min^{-1}) with UV analysis (Hewlett Packard 8453 diode array spectrophotometer). A media volume of 500 mL or 900 mL was used. The media was either phosphate buffer, pH 6.8 (indomethacin and tolbutamide), or 1% sodium dodecyl sulphate (SDS) in water (lacidipine and nifedipine). The pH of the SDS media was constant throughout the 60-min experiment at pH 6.4. A UV wavelength specific for each drug and free from interference with the PVP or PVP/VA spectrum was selected. Measurements were performed in triplicate.

Physical stability

Milled extrudate samples were stored for 4–8 weeks at 25°C/75% relative humidity (RH) and 25°C/ < 10% RH in environmentally-controlled incubators protected from light. Samples were characterized with DSC, MTDSC, XRPD and moisture analysis.

Results and Discussion

Melt extrusion has been performed with a number of drugs and different polymers (Gruenhagen 1996; Breitenbach et al 1998; Breitenbach 2000), but characterization of the products and physical stability upon storage have not been extensively described in the literature. Additionally, the effect of extrusion temperature on the type of dispersion formed by the extruder has received little attention. Initial temperatures for extrusion in this study were based on DSC determination of the drug melting points (indomethacin 162°C; lacidipine 185°C; nifedipine 175°C; and tolbutamide 130°C). However, it was expected that extrusion may be performed at temperatures below the melting point of the drug due to the presence of polymer and the input of shear stress from the twin-screw extruder.

The extrudates were produced as thin spaghetti-like strands and were visually inspected after manufacture. UV analysis of both extrudates and physical mixtures confirmed that the drug content was 98.0–101.3% of the expected range. No sign of smoke, which would indicate significant chemical degradation, was noticed at any of the melt extrusion temperatures used. Cooling was rapid and the indomethacin, lacidipine and nifedipine/PVP and PVP/VA (1:1) extrudates hardened quickly after extrusion. Indomethacin/PVP (4:1) and tolbutamide/PVP (1:1) extrudates hardened more slowly. The optical appearance of the extrudates is summarized in Table 2 and indicates that extrudates were transparent, cloudy or opaque. Figure 1a shows photographs taken after manufacture of the various extrudates.

Scanning electron micrographs showed that the external and internal (fracture surface) appearance of intact transparent extrudates, as well as the morphology of the transparent extrudates after milling, were consistent with glass solution formation with no signs of crystals present in the samples. Figure 1b (A) shows the transparent indomethacin/PVP (4:1) extrudate as an

Table 2 Characterization of drug/polymer extrudates.

Drug	Polymer	Ratio	Run[a]	Optical appearance[b]	Crystallinity XRPD (%)	Tg (°C)	% Water[e] (w/w)	Chemical degradation[f]
Indomethacin	PVP	1:1	A	T, yellow	–[d]	–	–	–
			B	T, yellow	–	77.2	1.6	< 1%
			C	T, yellow	–	–	–	–
			D	T, yellow	–	–	–	8.9%
	PVP	4:1	A	T, yellow	–	53.3	0.9	< 1%
			B	O, yellow	6.3	56.0	0.9	–
			C	Cloudy, yellow	1.0	51.9	0.9	–
			D	T, yellow	–	52.8	0.9	< 1%
	PVP/VA	1:1	A	T, yellow	–	63.8	1.2	< 1%
			B	T, yellow	–	–	–	–
			C	Cloudy[c], yellow	–	55.5	1.5	–
Lacidipine	PVP	1:1	A	T, yellow	–	78.4	2.5	1.9%
			B	Cloudy, yellow	1.1	81.3	2.5	–
	PVP/VA	1:1	A	T, yellow	–	76.1	1.1	< 1%
Nifedipine	PVP	1:1	A	T, yellow	–	79.0	1.9	1.4%
Tolbutamide	PVP	1:1	A	O, white	–	38.1	1.8	1.6%
			B	O, pale yellow	–	36.5	1.5	3.0%[g]
			C	O, white	–	35.7	1.9	1.8%

[a]See Table 1 for temperatures; [b]T = transparent, O = opaque; [c]slighty cloudy; [d]– = no crystallinity detectable with XRPD; [e]based on average of thermogravimetry and Karl Fischer analysis; [f]determined by HPLC as percentage reduction in drug peak; [g]colour change.

example. The opaque tolbutamide extrudate (Figure 1b, B) was porous, but also appeared homogeneous with no signs of crystals visible. The cloudy extrudates and the opaque indomethacin/PVP (4:1) extrudate had an irregular/rough external appearance, however crystalline particles were again difficult to detect (Figure 1b, C).

XRPD

XRPD was used to determine the crystallinity of the extrudates. The X-ray diffractograms of the extrudates were compared with those of crystalline drug and physical mixtures of drug and amorphous polymer. Peaks were apparent in both the physical mixtures and pure drug substances, but absent from the diffractograms of the transparent extrudates (Table 2). This indicates that the drug is present in the extrudate in the amorphous state. The opaque tolbutamide extrudates also showed no sign of crystallinity using XRPD. Diffractograms of the indomethacin/PVP (4:1) opaque extrudates Run B and the cloudy extrudates (lacidipine/PVP (1:1) Run B and indomethacin/PVP (4:1) Run C), showed peaks indicating the presence of crystalline drug, whereas no crystallinity was detected in the cloudy indomethacin/PVP/VA (1:1) Run C extrudate (Table 2).

Thermal analysis

Indomethacin drug substance exhibited a melting endotherm at 162.7 ± 1.4°C, with an enthalpy of 109.6 ± 5.2 J g^{-1} (Figure 2a, A). Lacidipine drug substance showed a melting endotherm at 184.8 ± 0.1°C, with an enthalpy of fusion of 99.8 ± 4.2 J g^{-1}. Nifedipine drug substance exhibited a melting endotherm at 175.2 ± 0.9°C, with an enthalpy of 106.7 ± 4.2 J g^{-1}. Tolbutamide drug substance showed a melting endotherm at 128.4 ± 0.3°C, with an enthalpy of 91.4 ± 3.0 J g^{-1}.

The physical mixtures of crystalline drugs and polymer showed a slight decrease in the melting temperature of the drug and a significant decrease in enthalpy of fusion, due to a combination of dilution of drug, miscibility of the two components on melting and interference from the water endotherm associated with the polymer (Figure 2a, B–D shows indomethacin as an example). The transparent extrudates exhibited a broad weak endotherm due to water dehydration (50–120°C), with no evidence of a drug melt (Figure 2a, E and F shows indomethacin as an example). The presence of a single glass transition could be detected accurately by MTDSC (Figure 2b shows indomethacin as an example) at an intermediate temperature between the Tg of the drugs and polymer (Table 2). The fact that only one Tg

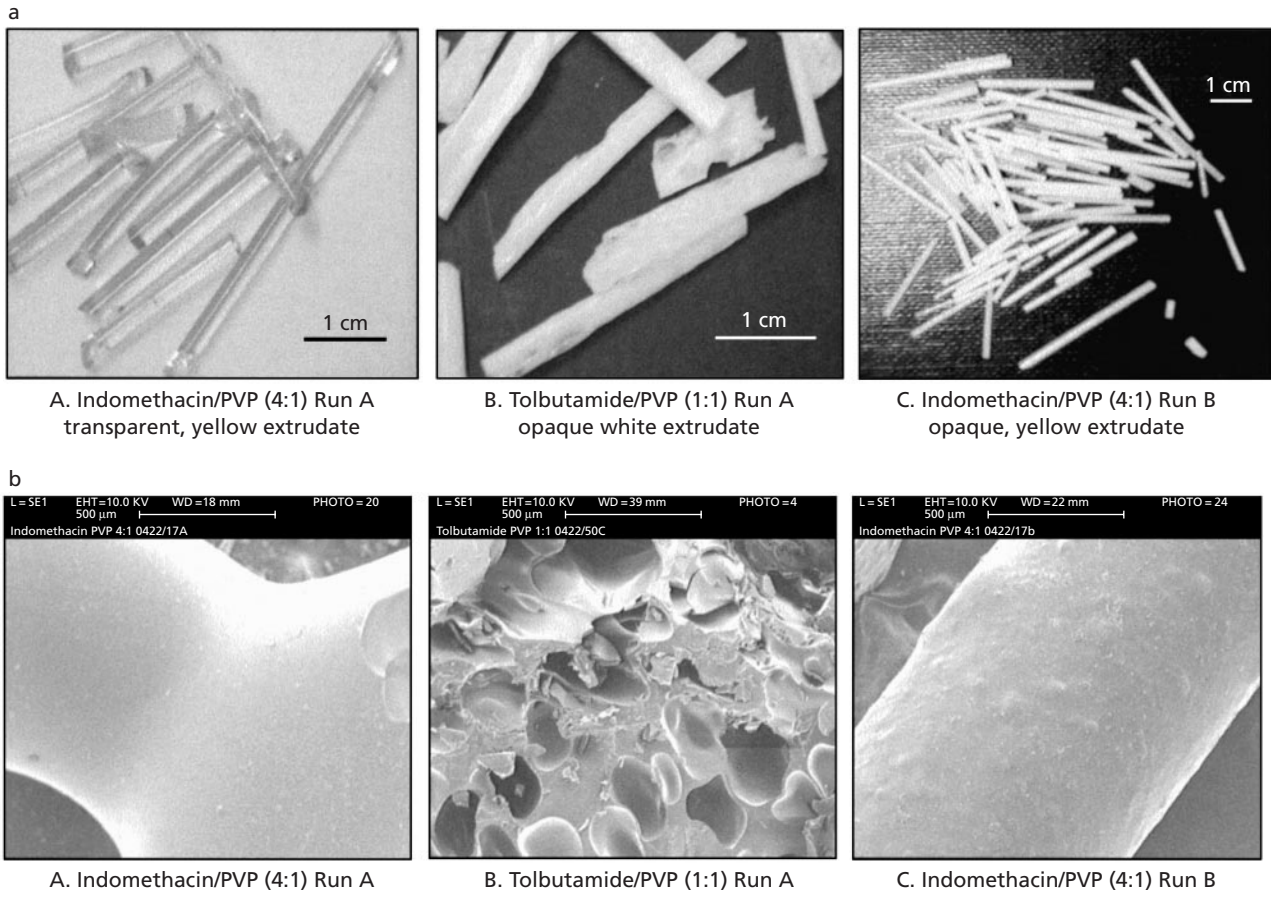

Figure 1 Photographs of extrudates (a) and scanning electron micrographs of intact extrudates (b).

is apparent indicates complete miscibility of the drugs and polymer when melt extruded (Lu & Zografi 1998). The extrudates were also XRPD amorphous and, thus, strong evidence was found for glass solution formation. The presence of crystalline drug in the PVP (4:1) Run B extrudate was demonstrated by the presence of an indomethacin melt endotherm at 149.5°C (17.2 J g^{-1}) and in lacidipine/PVP (1:1) extrudate Run B by the presence of a lacidipine melt endotherm at 170.8°C (1.5 J g^{-1}).

For indomethacin/PVP (4:1) extrudates, extrusion temperatures of 22°C (Run B) and 15°C (Run C) below the melting point of the drug did not form a completely amorphous dispersion, probably due to incomplete drug melts. Lacidipine/PVP extrudate also contained crystalline material when melt extruded 25°C below the drug melting point. However, amorphous dispersions of indomethacin/PVP (4:1) Run D were produced 12°C below the melting point of indomethacin, 37°C below the melting point of indomethacin for indomethacin/PVP/VA (1:1) Run C, and 8°C below the melting point of tolbutamide for tolbutamide/PVP (1:1) Run C.

The Tg is an important indicator of the stability of the amorphous state and it has been suggested that the Tg should be at least 50°C above the storage temperature to ensure stability over the shelf-life of the product (Yoshioka et al 1995). Therefore, an important part of the characterization of amorphous pharmaceuticals is Tg determination. Any water present in the extrudates absorbed after manufacture will have a plasticizing effect on the glass solution, significantly decreasing the Tg (Hancock & Zografi 1994). Table 2 summarizes the values for Tg of the extrudates, together with their water content directly after preparation. Provided moisture content does not increase after production, only indomethacin/PVP (1:1), lacidipine/PVP (1:1), lacidipine/PVP/VA (1:1) and nifedipine/PVP (1:1) have a Tg that would indicate sufficient stability for storage at 20°C.

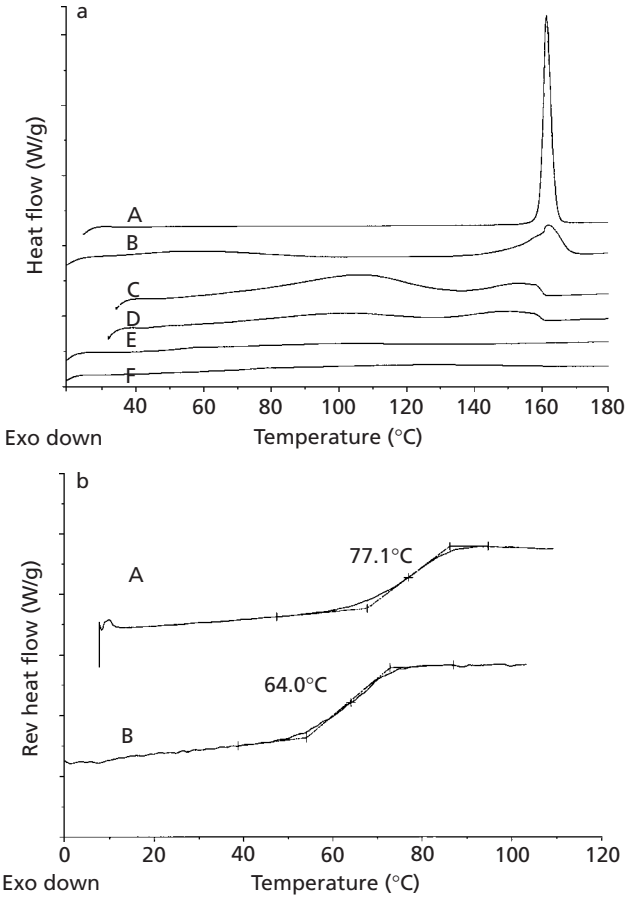

Figure 2 DSC thermograms of indomethacin (a). A. Drug; B. physical mixture/PVP (4:1); C. physical mixture/PVP (1:1); D. physical mixture/PVP/VA (1:1); E. extrudate/PVP/VA (1:1) Run A; F. extrudate/PVP (1:1) Run A. Reversing heat flow from modulated temperature DSC analysis of indomethacin extrudate Tg (b). A. Indomethacin/PVP (1:1) Run A; B. indomethacin/PVP/VA (1:1) Run A.

IR spectroscopy

The DRIFT spectra of the melt extrudates, compared with physical mixtures of crystalline drug and polymer, physical mixtures of amorphous drug and polymer, amorphous drug and crystalline drug are presented in Figures 3 and 4.

Indomethacin has been demonstrated to form hydrogen bonds (H-bonds) with PVP in solid dispersion prepared by co-evaporation, due to the interaction of its carboxylic group with the carbonyl group of PVP (Taylor & Zografi 1997). PVP can only act as a proton acceptor through either the carbonyl or C-N groups in the pyrrole ring. Therefore, to form a H-bond the drug must have a proton donor site. The presence of H-bonding has been linked to the physical stability of indomethacin/PVP amorphous dispersions (Taylor & Zografi 1997).

Figure 3 shows the DRIFT spectra for indomethacin drug substance, amorphous drug, crystalline drug/PVP (1:1) physical mixture, amorphous drug/PVP (1:1) physical mixture and drug/PVP (1:1) extrudate Run A. Indomethacin/PVP/VA samples showed similar spectra. DRIFT spectra of crystalline drug/PVP physical mixtures were equivalent to the addition spectrum of PVP and crystalline indomethacin. This indicates that no interaction occurs with simple physical mixing of crystalline drug and polymer (Figure 3). The spectrum of amorphous indomethacin was slightly less well defined than the spectrum of crystalline indomethacin, possibly indicating the lack of order associated with the amorphous state. The spectra of the amorphous indomethacin/PVP physical mixture showed differences from the crystalline drug/polymer mixture in the region of 1750 to 1600 cm^{-1}, due to changes in the indomethacin carboxylic and PVP carbonyl stretch. These differences may represent an interaction, as they are not apparent in the addition spectra of amorphous indomethacin and PVP (Figure 3). This finding differs from the result of Taylor & Zografi (1997), where no change in the spectra of amorphous indomethacin/PVP physical mixtures was reported. Only light grinding in a mortar and pestle was used to prepare the physical mixtures and KBr dispersions used in this study. However, it is apparent that some degree of H-bonding occurs between amorphous drug and polymer on mixing, which does not occur with crystalline drug. This interaction was more prominent with drug/polymer extrudate as the region relating to the PVP carbonyl stretch (1700 cm^{-1}) and indomethacin carboxylic group stretch (1600 cm^{-1}) were altered similarly to those reported as being due to H-bonding (Imaizumi et al 1983; Taylor & Zografi 1997). The same changes were noted with PVP/VA extrudates (data not shown). H-bonding interaction has also been demonstrated for both ibuprofen and sugars, with PVP (Sekizaki et al 1995; Taylor & Zografi 1998).

Figure 4 shows the IR spectra of tolbutamide crystalline drug, amorphous drug, crystalline drug/PVP physical mixture, amorphous drug/PVP physical mixture and extrudate. The crystalline drug/PVP physical mixture spectrum closely resembles that of the addition spectrum of the two components. After rapid cooling of the melt, tolbutamide is likely to be only partially amorphous, as rapid recrystallization occurs following the cooling of tolbutamide from beaker melts (Forster et al 1999). The DRIFT spectrum of partially amorphous tolbutamide is less well defined than that of the

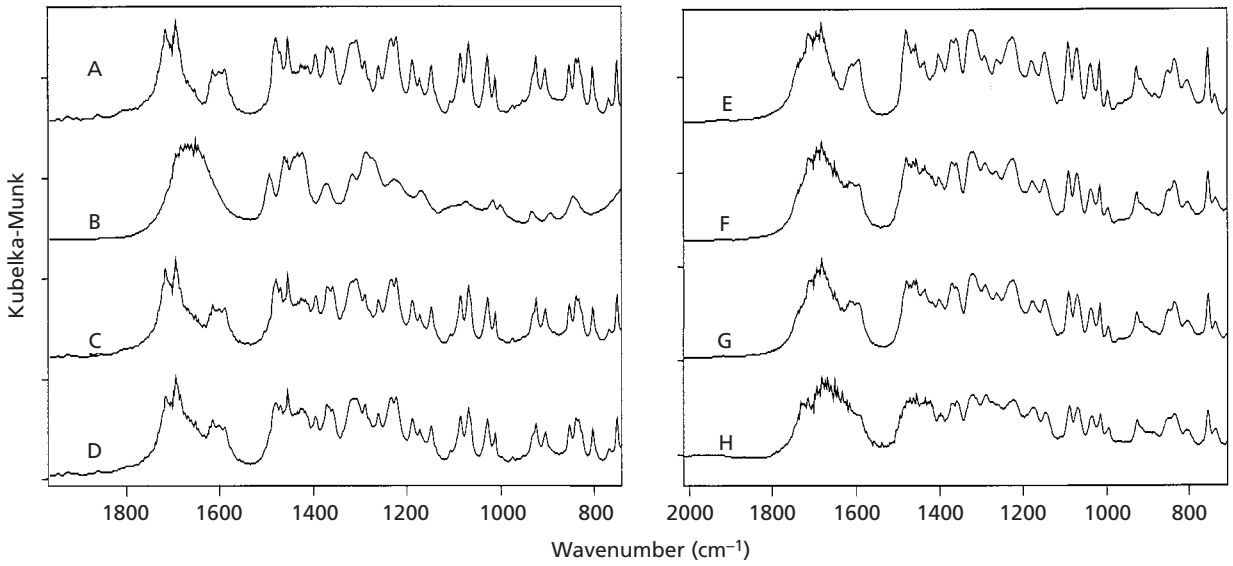

Figure 3 Diffuse reflectance infrared Fourier-transformed spectra of indomethacin. A. Crystalline drug; B. PVP; C. crystalline drug/PVP (1:1) physical mixture; D. addition spectra of crystalline drug and PVP; E. amorphous drug; F. amorphous drug/PVP (1:1) physical mixture; G. addition spectra of amorphous drug and PVP; H. drug/PVP (1:1) extrudate.

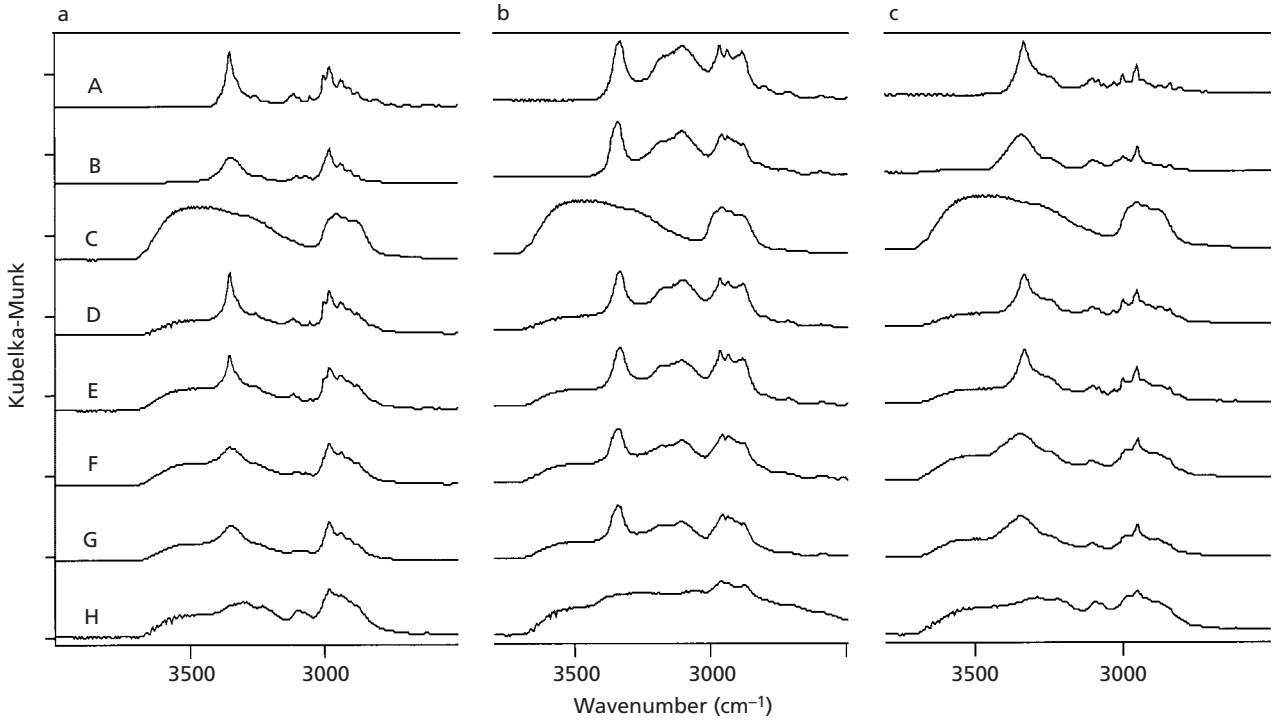

Figure 4 Diffuse reflectance infrared Fourier-transformed spectra of tolbutamide (a), lacidipine (b) and nifedipine (c). A. Crystalline drug; B. amorphous drug; C. PVP; D. crystalline drug/PVP (1:1) physical mixture; E. crystalline drug and PVP addition spectra; F. amorphous drug/PVP (1:1) physical mixture; G. amorphous drug and PVP addition spectra; H. drug/PVP (1:1) extrudate.

crystalline drug, but exhibits the same overall peak pattern. The spectrum of partially amorphous tolbutamide/PVP physical mixture is equivalent to the addition spectra of the two components. The spectrum of the extrudate, however, has a NH stretch ($\sim$ 3300 cm^{-1}) that is broad and weak compared with tolbutamide crystalline drug and there is a broad carbonyl stretch from 2500–3000 cm^{-1} that is characteristic of an intermolecular H-bond (Takla & Dakas 1989). Therefore, it can be concluded that tolbutamide/PVP extrudate also exhibits some degree of H-bonding to PVP through the amide groups. H-bonding between PVP and furosemide via the sulphonamide group of the drug and the carbonyl pyrrole group of PVP has been demonstrated previously (Doherty & York 1987). The spectra of lacidipine and nifedipine crystalline drugs, amorphous drugs, crystalline drug/polymer physical mixtures, amorphous drug/polymer physical mixtures and extrudates are also shown in Figure 4. Lacidipine and nifedipine have closely related chemical structures and, therefore, related DRIFT spectra. Again, in both cases the amorphous forms of the drug exhibit a less well defined version of the crystalline drug spectrum. The physical mixtures of drug and polymer resulted in spectra closely resembling the addition spectra of the individual components. In comparison, spectra of the extrudates show a significant change at 3338 and 3322 cm^{-1}, related to weakening or removal of the N–H stretching. This was also exhibited with lacidipine/PVP/VA extrudates (data not shown) and is strong evidence of H-bonding between the drug and polymer via the secondary amine group of both drugs. Another possibility is loss of the N–H stretch due to photodegradative dehydrogenation of these light-sensitive compounds (Teraoka et al 1999). However, this is unlikely as changes in the carbonyl stretching region (1684 cm^{-1}) of nifedipine previously reported upon light-induced decomposition were not found in this study (data not shown). Additionally, no changes were seen in the N–H stretch of physical mixtures. Moreover, during sample preparation and storage the lacidipine and nifedipine samples were protected from light.

The significant disappearance of N–H stretching with lacidipine, nifedipine and tolbutamide/polymer extrudates is strong evidence of H-bonding between these drugs and the polymer, as is the shift in the carboxylic group stretching of indomethacin. However, although all drug/polymer extrudates indicate the presence of H-bond formation, it is difficult to quantify the amount of H-bonding between compounds based on the DRIFT spectra or chemical structure. Previous studies suggest that indomethacin may show a greater degree of H-bonding than nifedipine. Nifedipine did not form an intermolecular H-bond in combination with phosphatidyl choline prepared by co-evaporation (Yamamura & Rogers 1996). In comparison, indomethacin, ketoprofen and flurbiprofen all form H-bonds with phosphatidyl choline (Fuji et al 1988).

Chemical stability

During the melt extrusion process both drug and polymer are subjected to heat and mechanical stress. The chemical stability of PVP and PVP/VA at temperatures below 200°C is well documented (Wade & Weller 1994). Therefore, only the drugs were assayed by HPLC for chemical decomposition. The amount of chemical decomposition is expressed as a reduction in the main drug peak area and shown in Table 2. Lacidipine and nifedipine extrudates showed less than 2% decomposition at all temperatures, which is additional evidence that the lacidipine and nifedipine samples were not subject to photodegradation. The only significant chemical degradation was seen for indomethacin/PVP (1:1) Run D extruded at 18°C above the melting point of indomethacin, and for tolbutamide/PVP (1:1) Run B, extruded at 20°C above melting point of tolbutamide (Table 2).

Dissolution

The dissolution of drug from extrudates compared with the drug alone and drug/polymer physical mixture is given in Table 3. Dissolution profiles of extrudates show an increase in dissolution rate compared with the physical mixtures and crystalline drug. The extent of the increase compared with crystalline drug varied (lacidipine/PVP/VA (1:1) extrudate showed a 22-fold increase in drug release after 10 min, whereas with tolbutamide/PVP (1:1) extrudate only a 1.4-fold increase was found after 10 min). The differences in dissolution enhancement probably reflect differences in the initial crystalline drug solubility (equilibrium solubility values: lacidipine < 0.05 mg mL^{-1}, water 25°C; tolbutamide 1.35 mg mL^{-1}, pH 6.8 buffer 37°C).

The presence of small amounts of crystalline drug in the extrudates did not have a noticeable effect on drug dissolution. The indomethacin/PVP (4:1) Run B extrudate with 6.3% crystalline drug still gave 100% drug dissolution in 60 min. The dissolution from physical mixtures was also increased compared with the pure crystalline drug substance except for tolbutamide/PVP

Table 3 Dissolution results of crystalline drugs, physical mixtures of crystalline drug and polymer and melt extrudates.

Compound	Polymer	Ratio	Form	Q10	Q60	Dissolution rate increase[a]	
						Q10	Q60
Indomethacin			Crystalline	27.3 ± 4.0	40.9 ± 3.5	–	–
	PVP	1:1	Extrudate	101.9 ± 0.9	99.2 ± 0.5	3.7	2.4
			Physical mixture	41.2 ± 7.9	65.0 ± 3.8	1.5	1.6
		4:1	Extrudate Run A	96.7 ± 1.2	101.8 ± 0.3	3.5	2.5
			Extrudate Run B	97.1 ± 0.3	99.9 ± 1.3	3.6	2.4
			Physical mixture	34.4 ± 10.0	51.9 ± 6.7	1.3	1.3
	PVP/VA	1:1	Extrudate	100.4 ± 7.0	101.8 ± 1.3	3.7	2.5
			Physical mixture	29.1 ± 0.1	60.8 ± 0.9	1.1	1.5
Lacidipine			Crystalline	3.8 ± 3.9	7.0 ± 4.3	–	–
	PVP	1:1	Extrudate Run A	75.3 ± 8.2	79.5 ± 8.2	19.8	11.4
			Extrudate Run B	72.0 ± 3.6	81.4 ± 2.3	18.9	11.6
			Physical mixture	5.3 ± 1.0	14.0 ± 2.0	1.4	2.0
	PVP/VA	1:1	Extrudate	83.5 ± 1.7	88.6 ± 1.9	22.0	12.7
			Physical mixture	5.7 ± 1.9	15.6 ± 6.11	1.5	2.2
Nifedipine			Crystalline	16.4 ± 1.9	21.5 ± 2.5	–	–
	PVP	1:1	Extrudate	35.6 ± 1.5	50.1 ± 1.0	2.2	2.3
			Physical mixture	34.8 ± 2.4	34.7 ± 0.93	2.1	1.6
Tolbutamide			Crystalline	62.3 ± 9.8	75.7 ± 5.9	–	–
			Extrudate	86.1 ± 2.1	83.8 ± 2.2	1.4	1.1
			Physical mix	58.2 ± 5.5	70.2 ± 1.1	0.9	0.9

[a]Increase compared with crystalline drug (n = 3). Q10 and Q60 are percentage drug release after 10 min and 60 min, respectively.

(1:1) physical mixture. Therefore, the gains in drug dissolution are likely to be due to a combination of the intimacy of mixing of drug and hydrophilic polymer and the amorphous state of the drug substance.

Physical stability

The extrudates were characterized after 4–8 weeks storage at 25°C/75% RH and 25°C/< 10% RH. The results are shown in Table 4. Except for indomethacin/PVP (1:1) and indomethacin/PVP/VA (1:1) extrudates, all extrudate samples exhibited crystallinity after storage at 25°C/75% RH. At 25°C/75% RH the water content of the samples was increased and consequently the Tg decreased compared with storage at 25°C/< 10% RH.

The increased stability of indomethacin/polymer (1:1) extrudates at 25°C/75% RH compared with the other drug extrudates may be explained with reference to the Tg and moisture contents. Indomethacin/PVP (1:1) extrudate had a significantly higher Tg than both lacidipine and tolbutamide extrudates after storage at 25°C/75% RH. With Tg at 75% RH of 19.7°C and 4.4°C, respectively, lacidipine and tolbutamide extrudates were both in the rubbery amorphous state at 25°C. The rubbery state is associated with a decrease in viscosity and a corresponding increase in molecular mobility, which increases the probability of recrystallization (Hancock & Zografi 1997). The Tg of nifedipine/PVP extrudate was just above the temperature of storage but 10°C below the Tg of indomethacin/PVP (1:1), despite the fact that the initial Tg of indomethacin/PVP and nifedipine/PVP were almost identical (77°C and 79°C). Nifedipine extrudate thus shows marked crystallinity after 5 weeks storage at 75% RH. The reason for the larger decrease in Tg upon storage was that the water content of the nifedipine extrudate was greater than for the indomethacin extrudate at 25°C/75% RH. The increased moisture content of nifedipine extrudate could be linked to the degree of interaction (i.e. H-bonding) between drug and polymer, as less H-bonding between drug and polymer could make more H-bonding sites available to water (Jans-Frontini & Mielck 1996).

The importance of moisture content was confirmed with respect to the other extrudates. For example, the lacidipine/PVP/VA extrudate showed some crystallinity after 4 weeks storage at 25°C/75% RH. In

Table 4 Characterization of extrudates after storage (8 weeks).

Drug	Polymer	Storage condition[b]	Ratio	Run[c]	Tg (°C)	Water (%, w/w)	Crystallinity (%)
Indomethacin	PVP	1	1:1	A	36.1	7.4	–[d]
		2		A	75.1	1.8	–
	PVP	1	4:1	A	43.3	2.1	5.7
		2		A	60.4	0.5	–
	PVP/VA	1	1:1	A	47.4	3.3	–
		2		A	63.8	1.0	–
Lacidipine	PVP	1	1:1	A	19.7	13.0	21.5
		2		A	86.2	1.8	–
		1		B	–	12.9	21.8
		2		B	89.4	2.3	1.4
	PVP/VA[a]	1	1:1	A	43.2	6.2	2.7
		2		A	73.6	1.1	–
Nifedipine	PVP	1	1:1	A	26.1	11.6	24.0
		2		A	74.5	2.3	–
Tolbutamide	PVP	1	1:1	A	4.4	11.7	12.0
		2		A	45.5	1.5	–

[a]Four weeks storage only; [b]1 = 25°C/75% RH; 2 = 25°C/< 10% RH; [c]see Table 1 for temperatures; [d]– = no crystallinity detectable with XRPD.

comparison, indomethacin/PVP/VA (1:1) extrudate was stable for 8 weeks under the same conditions. The Tg of the lacidipine/PVP/VA extrudate was decreased by 33°C on storage, whereas the Tg of indomethacin/PVP/VA extrudate was decreased by only 16°C (Table 4). The moisture content of the lacidipine extrudate is twice that of the indomethacin extrudate. Again, this may be related to a different degree of H-bonding between drugs and polymer.

Lacidipine/PVP (1:1) extrudate Run B exhibited crystalline content immediately after extrusion (1.1%), and after 8 weeks storage at 25°C/75% RH an increase in crystalline content was noted (21.8%). Interestingly, this value is only slightly higher than the crystalline content exhibited by lacidipine/PVP (1:1) Run A (Table 4), which was a glass solution after melt extrusion. At 25°C/< 10% RH the increase in crystallinity of lacidipine/PVP (1:1) Run B was less than the error associated with the XRPD quantification method. These findings suggest that a small concentration of seed crystals does not have a marked effect on recrystallization under these storage conditions.

Summary

Melt extrusion of four poorly water-soluble drugs with PVP and PVP/VA resulted in glass solution formation depending on the temperature of melt extrusion. When the temperature of extrusion was too low, crystallinity was detected both visually and by XRPD and DSC indicating incomplete melting of the drug. A transparent and brittle melt extrudate is a strong indicator of glass solution formation, whereas a cloudy or an opaque extrudate could indicate crystalline material. However, it must be noted that physicochemical characterization should be used to confirm the conclusions from visual inspection of the extrudate. Tolbutamide melt extrudates were opaque, but were glass solutions.

Tolbutamide and indomethacin produced glass solutions at melt extrusion temperatures well below the melting point of the drug. This may relate to lower melting point of these two compounds in comparison with lacidipine and nifedipine. A compound with a lower melting point will have an increased plasticizing effect on amorphous polymers. Chemical stability during melt extrusion was high for all four drugs after melt extrusion. However, when the extrusion temperature was increased well above the melting point of indomethacin, significant chemical decomposition was noted. All extrudates gave an increased dissolution rate compared with both physical mixtures of drug/polymer and crystalline drug alone.

All extrudates exhibited some degree of H-bonding with PVP. Only indomethacin demonstrated H-bonding in amorphous drug/PVP mixtures. Physical stability of the melt extrudates was related to moisture content and

Tg. At high humidity (75% RH) indomethacin extrudates were more physically stable than lacidipine, nifedipine and tolbutamide extrudates, which all showed a more substantial decrease in Tg and increased moisture content compared with indomethacin extrudates. It can be speculated that the amount of H-bonding between drug and polymer determines the amount of moisture that is taken up by the sample and thus the physical stability. However, from the presence of H-bonding indicated by IR spectroscopy alone, it should not be concluded that the stability of the glass solution is high. Future investigations should aim at quantifying the degree of H-bonding between drug and polymer to improve predictions on physical stability of melt extrudates.

References

Ali, S. L. (1989) Nifedipine. In: Florey, K. (ed.) *Analytical Profiles of Drug Substances*, Vol. 18. Academic Press, New York

Breitenbach, J. (2000) Feste lösungen durch schmelzextrusion – ein integriertes herstellknozept. *Pharm. Unserer Zeit*. **29**: 46–49

Breitenbach, J., Berndl, G., Neumann, J., Rosenberg, J., Simon, D., Zeidler, J. (1998) Solid dispersions by an integrated melt extrusion system. *Proc. Control. Rel. Soc.* **25**: 804–805

Corrigan, O. I. (1985) Mechanisms of dissolution of fast release solid dispersions. *Drug Dev. Ind. Pharm.* **11**: 697–724

Craig, D. Q. M., Royall, P. G. (1998) The use of modulated temperature DSC for the study of pharmaceutical systems: potential uses and limitations. *Pharm. Res.* **15**: 1152–1153

Doherty, C., York. P. (1987) Evidence for solid- and liquid-state interactions in a furosemide-polyvinylpyrrolidone solid dispersion. *J. Pharm. Sci.* **76**: 731–737

Ford, J. L. (1986) The current status of solid dispersions. *Pharm. Acta Helv.* **61**: 69–88

Forster, A. H., Hempenstall, J., Tucker, I., Rades, T. (1999) Selection of drug candidates for melt extrusion by thermal methods. *Proc. Aust. Pharm. Sci. Assoc.* **64**

Fuji, M., Terai, H., Mori, T., Sawada, Y., Matsumoto, M. (1988) The properties of solid dispersions of indomethacin, ketoprofen and flurbiprofen in phosphatidylcholine. *Chem. Pharm. Bull.* **36**: 2186–2219

Gruenhagen, H. H. (1996) Polymer/drug-melt extrusion: therapeutic and technological. Appeal. *Pharm. Technol. Eur.* **11**: 22–27

Hamza, Y., Samour, O. A., Abdel-Latif, H. A. (1994) Enhancement of dissolution of indomethacin and modulation of its pharmacodynamics and ulcerogenicity via solid dispersions. *Pharm. Ind.* **56**: 286–291

Hancock, B. C., Zografi, G. (1994) The relationship between the glass transition temperature and the water content of amorphous pharmaceutical solids. *Pharm. Res.* **11**: 471–477

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

Hülsmann, S., Backenseld, T., Keitel, S., Bodmeier, R. (2000) Melt extrusion – an alternative method for enhancing the dissolution rate of 17β-estradiol hemihydrate. *Eur. J. Pharm. Biopharm.* **49**: 237–242

Imaizumi, H., Nambu, N., Nagai, T. (1983) Stabilization of amorphous state of indomethacin by solid dispersion in polyvinylpyrrolidone. *Chem. Pharm. Bull.* **31**: 2510–2512

Jans-Frontini, H., Mielck, J. B. (1996) Stability of drugs in solid dispersions: effect of glass transition on degradation kinetics under stress in systems of reserpine and PVP. *Eur. J. Pharm. Biopharm.* **42**: 303–312

Kearney, A. S., Gabriel, D. L., Mehta, S. C., Radebaugh, G. W. (1994) Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the antiinflammatory CI-987. *Int. J. Pharm.* **104**: 169–174

Lu, Q., Zografi, G. (1998) Phase behaviour of binary and tenary amorphous mixtures containing indomethacin, citric acid, and PVP. *Pharm. Res.* **15**: 1202–1206

Miralles, M. J., Mcginity, J. W., Martin, A. (1982) Combined water-soluble carriers for co-precipitates of tolbutamide. *J. Pharm. Sci.* **71**: 302–304

Sekizaki, H., Danjo, K., Eguchi, H., Yonezawa, Y., Sunada, H., Otsuka, A. (1995) Solid-state interaction of ibuprofen with polyvinylpyrrolidone. *Chem. Pharm. Bull.* **43**: 988–993

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

Shamblin, S. L., Zografi, G. (1999) The effects of absorbed water on the properties of amorphous mixtures containing sucrose. *Pharm. Res.* **16**: 1119–1124

Takla, P. G., Dakas, C. J. (1989) An infrared study of tautomerism in acetohexamide polymorphs. *J. Pharm. Pharmacol.* **41**: 227–230

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

Taylor, L. S., Zografi, G. (1998) Sugar-polymer hydrogen bond interactions in lyophilized amorphous mixtures. *J. Pharm. Sci.* **87**: 1615–1621

Teraoka, R., Otsuka, M., Matsuda, Y. (1999) Evaluation of photostability of solid-state dimethyl 1,4-dimethyl-4-(2-nitro-phenyl)-3,5-pyridinedicarboxylate by using Fourier-transformed reflection-absorption infrared spectroscopy. *Int. J. Pharm.* **184**: 35–43

Wade, A., Weller, P. J. (1994) *Handbook of Pharmaceutical Excipients*. American Pharmaceutical Association, Washington; Pharmaceutical Press, London

White, J. L., Szydlowski, W., Min, K., Kim, M. H. (1987) Twin screw extruders; development of technology and analysis of flow. *Adv. Polym. Technol.* **7**: 295–332

Yamamura, S., Rogers, J. A. (1996) Characterization and dissolution behaviour of nifedipine and phosphatidylcholine binary systems. *Int. J. Pharm.* **130**: 67–73

Yoshioka, M., Hancock, B. C., Zografi, G. (1994) Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *J. Pharm. Sci.* **83**: 1700–1705

Yoshioka, M., Hancock, B. C., Zografi, G. (1995) Inhibition of indomethacin crystallization in poly(vinylpyrrolidone) coprecipitates. *J. Pharm. Sci.* **84**: 983–986