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International Journal of Pharmaceutics 226 (2001) 147–161

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Selection of excipients for melt extrusion with two poorly water-soluble drugs by solubility parameter calculation and thermal analysis

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Received 9 April 2001; received in revised form 2 July 2001; accepted 3 July 2001

Abstract

The aim of this study was to determine the miscibility of drug and excipient to predict if glass solutions are likely to form when drug and excipient are melt extruded. Two poorly water-soluble drugs, indomethacin and lacidipine, were selected along with 11 excipients (polymeric and non-polymeric). Estimation of drug/excipient miscibility was performed using a combination of the Hoy and Hoftzyer/Van Krevelen methods for Hansen solubility parameter calculation. Miscibility was experimentally investigated with differential scanning calorimetry (DSC) and hot stage microscopy (HSM). Studies were performed at drug/excipient ratios, 1:4, 1:1 and 4:1. Analysis of the glass transition temperature (T_g) was performed by quench cooling drug/excipient melts in the DSC. Differences in the drug/excipient solubility parameters of < 7.0 MPa$^{1/2}$ were predicted to indicate significant miscibility and, therefore, glass solution formation on melt extrusion. In comparison, differences of > 10 MPa$^{1/2}$ were expected to indicate a lack of miscibility and not form glass solutions when melt extruded. Experimentally, miscibility was shown by changes in drug/excipient melting endotherms and confirmed by HSM investigations. Experimental results were in agreement with solubility parameter predictions. In addition, drug/excipient combinations predicted to be largely immiscible often exhibited more than one T_g upon reheating in the DSC. Melt extrusion of miscible components resulted in amorphous solid solution formation, whereas extrusion of an 'immiscible' component led to amorphous drug dispersed in crystalline excipient. In conclusion, combining calculation of Hansen solubility parameters with thermal analysis of drug/excipient miscibility can be successfully applied to predict formation of glass solutions with melt extrusion.

Keywords: Melt extrusion; Drug/excipient interactions; Indomethacin; Lacidipine; Solubility parameters; Thermal analysis

1. Introduction

Increasing the dissolution rate of poorly water-soluble drugs is one of the major challenges in dosage form development. One approach is the

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0378-5173/01/$ - see front matter
PII: S0378-5173(01)00801-8

formation of a solid dispersion of drug with a hydrophilic excipient. The ideal type of solid dispersion for increasing dissolution is a glass solution, in which the amorphous drug has a lower thermodynamic barrier to dissolution together with a maximally reduced particle size (Hancock and Zografi, 1997). In addition, the intimate presence of a hydrophilic excipient can increase wetting and lead to super-saturation in the diffusion layer (Chiou and Riegelman, 1971; Shefter, 1981; Ford, 1986). A glass solution is formed when two or more components are entirely miscible in the molten state and cool to form an amorphous one-phase system. However, to form a glass solution that is physically stable over prolonged periods of time the glass transition temperature (T_g) should be higher than the storage temperature. Hancock and Zografi (1997) suggest that the T_g should be at least 50 °C above the storage temperature to ensure that the product remains stable over its shelf-life.

A number of studies have recently shown the potential of melt extrusion to form glass solutions of drug and excipient (Gruenhagen, 1996; Breitenbach, 2000; Breitenbach et al., 1998; Forster et al., 2001). Melt extrusion has advantages over solvent based methods of forming glass solutions, including ease of use, decreased environmental implications, absence of residual solvents, decreased costs and the possibility of continuous processing (Gruenhagen, 1996). To date most pharmaceutical research with melt extrusion has focused on the use of thermoplastic polymers as carriers, such as polyvinylpyrrolidone (PVP) and polymethacrylates (Gruenhagen, 1996; Repka et al., 1999; Breitenbach, 2000). However, an extensive number of excipients including cellulose derivatives, sugars and sugar alcohols have been investigated as potential carriers using solid dispersion preparation methods other than melt extrusion (Chiou and Riegelman, 1971; Ford, 1986; Hatley, 1997; Suzuki and Sunada, 1998; Serajuddin, 1999).

Laboratory-scale melt extruders require considerable quantities of drug substance, which are not often available at the early developmental stage when pilot formulation studies are undertaken. Therefore, the aim of the current investigation was to evaluate ways to predict if a glass solution was likely to be formed when a particular drug and excipient mixture was melt extruded at a specific drug/excipient ratio using minimal quantities of drug. In this study, prediction was based on comparison of the solubility parameters of drug and excipient, experimental determination of miscibility by differential scanning calorimetry (DSC) and hot stage microscopy (HSM), and analysis of the glass transition temperature (T_g) of rapidly cooled drug/excipient melts. Analysis of the T_g is useful for two reasons; comparison of the T_g to the normal storage temperature (20–30 °C) allows prediction as to whether the melt extrudate will be in the glassy or rubbery state. Secondly, a single T_g at an intermediate temperature between the T_g of both amorphous components, is further evidence of a miscible system (Lu and Zografi, 1998). The Gordon–Taylor equation states that the T_g of an ideally mixed solid solution will be a sum of the weight fraction, thermal expansion and T_g of the individual components (Schneider, 1989).

Indomethacin and lacidipine were used in this study as model drugs. Both compounds are poorly water-soluble and have shown increased dissolution when melt extruded with PVP (Forster et al., 2001).

2. Experimental

2.1. Materials

Indomethacin, polyethylene glycol 8000 (PEG 8, average MW 7000–9000), polyethylene glycol 10 000 (PEG 10, average MW 8500–11 500), polyvinyl alcohol (PVA) and polyvinylpyrrolidone k12 (PVP 12, average MW 2500) were obtained from Sigma Chemicals (Dorset, UK). Lacidipine, citric acid, glucose, lactose anhydrous, mannitol, polyvinylpyrrolidone k30 (PVP 30, average MW 50000) and sucrose anhydrous, were provided by GlaxoSmithKline (Ware, UK). Polyvinylpyrrolidone-co-vinyl-acetate (PVP/VA, MW 45 000–70 000) was obtained from ISP (Manchester, UK). All chemicals were of laboratory reagent grade. Experiments with lacidipine were performed under subdued light.

2.2. Solubility parameter calculation

The Hansen solubility parameters of the compounds were calculated from the chemical structures using the approaches of Hoftyzer/Van Krevelen, and Hoy (Van Krevelen, 1990). As an example, the calculations carried out for lacidipine are given in Fig. 1. For polymeric excipients determination of the solubility parameter was based on the average molecular weight. The units of solubility parameters are $MPa^{1/2}$, $(J\ m^{-3})^{1/2}$ or $(cal\ cm^{-3})^{1/2}$, where 1 $(cal\ cm^{-3})^{1/2}$ is equivalent to 2.0421 $MPa^{1/2}$ (Hancock et al., 1997).

2.3. Preparation of physical mixtures

A series of physical mixtures of drug and excipient were prepared at three mass ratios, 1:4, 1:1 and 4:1, by gently grinding accurately weighed quantities using a mortar and pestle for 2 min. Homogeneity of mixing was considered uniform when three separate DSC thermograms were similar when superimposed. The enthalpy of fusion for all mixtures at all mass ratios had an average coefficient of variation of 4.7%.

2.4. Differential scanning calorimetry

A TA Instruments DSC 2920 (Surrey, UK) was used at 10 K min^{-1} with a nitrogen purge at 20 ml min^{-1}. Preparation of melts and determination of miscibility were performed using crimped aluminium sample pans with a pierced lid and a sample size of 5–10 mg. An empty pan was used for reference and calibrations for temperature and enthalpy were performed routinely with indium (Laboratory of the Government Chemist, Middlesex, UK).

The T_g of individual components and drug/excipient blends was determined by melting the sample in the DSC and rapidly cooling the melt by placing a stainless steel holder filled with liquid nitrogen over the DSC cell ('quench cooling'). This method has been used successfully to prepare glasses of both indomethacin and lacidipine (Forster et al., 1999). The cooled melt was then reheated in the DSC and the T_g noted. With this method, the effect of moisture is removed, as all blends were heated in pierced pans to at least 150 °C using dry nitrogen purge gas.

For melt extrudates water absorbed after manufacture made accurate analysis of the T_g difficult. Therefore, modulated temperature DSC (MTDSC) was used as this approach separates thermodynamically reversing events (e.g. T_g), from non-reversing events (e.g. dehydration) (Craig and Royall, 1998). MTDSC was performed using the TA Instruments DSC 2920 with a liquid nitrogen cooling accessory. Samples (5–10 mg) were sealed in aluminium pans without a pinhole in the lid. A linear heating rate of 2 K min^{-1} with an oscillation of ± 0.25 K every 40 s was applied, ensuring at least six modulations per thermal event. Calibration of the MTDSC was performed for temperature and enthalpy at 2 K min^{-1} using indium.

2.5. Hot stage microscopy

A Linkam TMS 92 hot stage (Surrey, UK) and Olympus light microscope with a JVC video-link and Image Pro Plus software (Media Cybernetics, Silver Spring, USA) were used to investigate drug/excipient miscibility. The heating rate was 10 K min^{-1}. Cross-polarisation was used to investigate crystallinity.

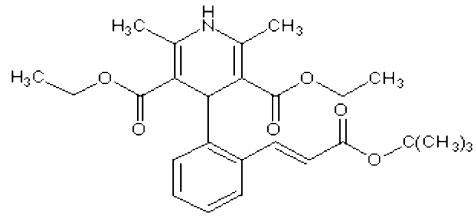
2.6. Thermogravimetric analysis

Thermal decomposition of some drug/excipient mixtures was investigated using a TA Instruments 2950 Hi-res TGA at a heating rate of 10 K min^{-1} and a nitrogen flow of 100 ml min^{-1}. Samples (20–30 mg) were heated until weight loss was detected. Temperature was calibrated by measuring the Curie point of nickel and alumel (TA Instruments) at 10 K min^{-1}.

TGA was also used to determine the moisture content of the melt extrudates. Weight loss up to 150 °C was taken as dehydration and the weight change equivalent to moisture content.

2.7. X-ray powder diffraction

X-ray powder diffraction (XRPD) was performed on a Philips X'pert MPD with a count



$$\delta_d = \frac{\sum F_{di}}{V} = \frac{6960}{378.4} = 18.4$$

Group$_z$	F_{di}	F^2_{pi}	E_{hi}	$\Sigma^z V/cm^3\ mol^{-1}$
(7) CH_3	2940	0	0	234.5
(2) CH_2	540	0	0	32.2
(1) NH	160	210	3100	4.5
(1) C	-70	0	0	-19.2
(1) CH	80	0	0	-1.0
(4) C=	280	0	0	-22
(1) Phenylene	1270	110	0	52.4
(2) HC=	400	0	0	27
(3) COO	1170	1470	21000	54
(1) ring (6)	190	-	-	16
Σ	**6960**	**1790**	**24100**	**378.4**

$$\delta_p = \frac{\sqrt{\sum F_{pi}^2}}{V} = \frac{\sqrt{1790}}{378.4} = 0.11$$

$$\delta_h = \sqrt{\frac{\sum E_{hi}}{V}} = \sqrt{\frac{24100}{378.4}} = 7.98$$

$$\delta_t = \sqrt{\delta_d{}^2 + \delta_p{}^2 + \delta_h{}^2} = 20.1$$

(a) Hoftyzer and Van Krevelen

z is the functional group, F_{di} is the group dispersion component giving δ_d, F^2_{pi} the group polar component, E_{hi} the hydrogen bonding component and V the molar volume from Hildebrand analysis (Fedors, 1974). δ_t is the total solubility parameter calculated from the various components (dispersion forces δ_d, hydrogen bonding δ_h and polar interactions δ_p).

Group$_z$	F_t	F_p	Δ_T	V
(7) CH_3	2124.5	0	0.161	150.85
(2) CH_2	538	0	0.04	31.1
1) NH	368	368	0.031	11.0
(1) C	65.5	0	0	3.56
(1) CH	176.0	0	0.012	9.56
(4) C=	692	252	0	28.72
(1) Phenylene	20.2	-13.3	0	-
(2) HC=	498	119	0.036	26.36
(3) COO	1920	1584	0.141	71.1
(1) ring (6)	-48	61	0	-
(5) CH_{ar}	1205	312.5	0.055	67.1
(1) C_{ar}	201	65	0.011	7.42
Σ	**7760.2**	**2748.2**	**0.487**	**406.8**

$$\delta_t = \frac{F_t + B}{V} = \frac{7760.2 + 277}{406.8} = 19.8$$

$$Base = 277$$

(b) Hoy

F_t is the molar attraction constant, F_p the polar component, Δ_T the Lyderson correction for non-ideality, V the molar volume and *Base* is a constant. Note, only the calculation for $\delta_{t(total)}$ is given in figure.

Fig. 1. Solubility parameter calculations for lacidipine.

time of 1 s and step size of 0.02° 2θ using Ni filtered Cu-Kα radiation (50 kV and 40 mA). Back filled samples were prepared using approximately 300 mg of powder.

2.8. Scanning electron microscopy

Samples were coated with a thin gold-palladium layer by sputter coating (Bio-rad E5100, Watford, UK) and investigated with a Cambridge S360 Scanning Electron Microscope (SEM, Cambridge, UK), which was operated with an acceleration voltage of 10 kV.

2.9. Melt extrusion

Drug and excipient blends were prepared by mixing accurately weighed quantities of drug and excipient in a plastic bag for 5 min. Extrusion was performed in a low humidity ($<25\%$ RH) and controlled temperature (20 °C) environment using a Brabender Plasti-corder PL2000 (Duisburg, Germany) with counter-rotating intermeshing twin screws (diameter 3 and 1/4 in., L/D ratio 18). The heating barrel is divided into four temperature zones. For each drug/excipient blend, the first zone ('throat') was initially heated by conduction and then cooled to 20 °C using a water cooler to avoid plasticised material blocking flow through the machine. Zones 2–4 were kept at a constant temperature for each drug/excipient blend. The following extrusion temperatures were used; indomethacin/PVP 30 (1:1) 155 °C, (4:1) 150 °C, indomethacin/PVP/VA (1:1) 150 °C, lacidipine/PVP 30 (1:1) 180 °C, (1:4) 175–200 °C, lacidipine/PVP/VA (1:1) 170 °C, lacidipine/mannitol (1:1) 185 °C. The screw speed was adjusted to 20–30 rpm, and the extrudate was cooled on a conveyer belt.

The extrudate was reduced in particle size by milling in a hammer mill through a 0.5-mm screen. A particle size range of 25–250 μm was selected for analysis.

3. Results and discussion

3.1. Solubility parameter calculation

Estimates of the solubility parameter (δ) have been used with some success to predict the miscibility of drugs and excipients (Suzuki and Sunada, 1997; Greenhalgh et al., 1999; Hancock et al., 1997). Greenhalgh et al. (1999) used Hildebrand solubility parameters, which account for the dispersive forces (E_d). The same authors suggested that interactions between polar (E_p) and hydrogen bonding groups (E_h), which also may affect solubility, should be incorporated in the estimation of the solubility parameter. These values are combined in the Hansen solubility parameter (Greenhalgh et al., 1999), which can be estimated based on the methods of Hoftyzer/Van Krevelen and Hoy (Van Krevelen, 1990). In this study the average of the Hoftyzer/Van Krevelen and Hoy values have been used to calculate δ (Table 1).

Compounds with similar values for δ are likely to be miscible. This is because the energy of mixing released by interactions within the components is balanced by the energy released by interaction between the components (Greenhalgh et al., 1999). Greenhalgh et al. (1999) classified excipients based on the difference between the solubility parameters of excipients and drugs ($\Delta\delta$). The authors demonstrated that compounds with a $\Delta\delta < 7.0$ $MPa^{1/2}$ were likely to be miscible. When the $\Delta\delta > 10$ $MPa^{1/2}$ the compounds were likely to be immiscible. Since the values for δ are fairly similar for indomethacin and lacidipine (22.1 $MPa^{1/2}$ and 20.0 $MPa^{1/2}$, respectively), it can be predicted that an excipient with a δ less than 27–29 $MPa^{1/2}$ should show some miscibility with both drugs, whereas an excipient with a δ over 30–32 $MPa^{1/2}$ is likely to be immiscible.

From the results summarised in Table 1 the excipients in this study can be grouped into three categories based on the $\Delta\delta$. Excipients with a $\Delta\delta < 2.0$ $MPa^{1/2}$ are termed 'group 1' and are likely to be miscible and form glass solutions when melt extruded with both drugs. Those excipients with $\Delta\delta > 10$ $MPa^{1/2}$ are termed 'group 3' and are likely to be significantly immiscible and are not expected to form glass solutions. Citric acid is classified as 'group 2' and may show some miscibility with indomethacin since the $\Delta\delta$ is 5.6. Lacidipine is less likely to be miscible with citric acid since the $\Delta\delta$ is 7.7 $MPa^{1/2}$. PVA is also classified as 'group 2' with

respect to indomethacin as the $\Delta\delta$ is 8.9 $MPa^{1/2}$, but as 'group 3' with respect to lacidipine as the $\Delta\delta$ is 11.0 $MPa^{1/2}$.

3.2. Thermal analysis of miscibility

Miscibility is detected in the DSC by changes in the melting endotherm of the drug (Ford and Timmins, 1987; Mura et al., 1998). Analysis of the melt endotherm onset temperature (T_{mo}) and heat of fusion were used in this study to investigate miscibility. DSC was complemented by HSM, which allows visualisation of both melting events and dissolution of one component in the melt of the other. It must be noted that melt endotherms may be a mixture of the heat of fusion and heat of solution, but that these two events cannot be resolved with DSC (Ford and Timmins, 1987). Table 2 gives the T_{mo} and heats of fusion for drugs and excipients. In the case of PVP 12, PVP 30 and PVP/VA the T_{mo} and heats of fusion are not reported, as the polymers are completely amorphous. PVA is a partially amorphous polymer and, therefore, has a low value for heat of fusion (Van Krevelen, 1990). The heat of fusion for lactose anhydrous could not be experimentally determined due to degradation on melting.

Thermal investigation indicated strong evidence for miscibility of both drugs with PEG 8 and PEG 10. Fig. 2a shows the DSC thermograms for lacidipine/PEG 10 and clearly shows that the T_{mo} and heat of fusion of the drug are decreased with increasing PEG 10. Fig. 3a shows that lacidipine begins to dissolve in molten PEG 10 well before the melting point of drug alone.

Decreases in T_{mo} indicated that PVP 12 and PVP/VA were miscible with both drugs and that indomethacin was also miscible with PVP 30. These findings were supported with HSM (Fig. 3b). For lacidipine/PVP 30 at all mass ratios the T_{mo} remained unchanged, indicating a lack of miscibility (Table 3). However, HSM of lacidipine/PVP 30 (1:1) demonstrated that PVP 30 begins to dissolve in the molten lacidipine at around 180 °C (Fig. 3c).

Table 1
Solubility parameters of drugs and excipients

Compound	Solubility parameters (δ)			Group[a]
	Hoftyzer/Van Krevelan $(MPa)^{1/2}$	Hoy $(MPa)^{1/2}$	Average[b]	
Indomethacin	22.3	21.9	22.1	–
Lacidipine	20.1	19.8	20.0	–
PEG 8	21.6	21.6	21.6	1
PEG 10	21.5	21.6	21.6	1
PVP 12	22.4	20.7	21.3	1
PVP 30	22.4	20.7	21.6	1
PVP/VA[c]	21.5	20.6	21.1	1
PVA	31.7	30.3	31.0	2/3
Citric acid	29.4	25.9	27.7	2
Glucose	38.9	37.8	38.4	3
Mannitol	39.1	38.7	38.9	3
Lactose	35.7	33.0	34.4	3
Sucrose	36.0	33.5	34.8	3

Group 1 compounds likely to be miscible with indomethacin and lacidipine. Group 2 compounds likely to be immiscible with indomethacin and lacidipine. Group 3 borderline miscibility.

[a] Where the difference in solubility parameter (average) between drug and excipient is, group 1 < 2.0 $MPa^{1/2}$, group 2 = 5–8.9 $MPa^{1/2}$ and group 3 > 10.0 $MPa^{1/2}$.

[b] Is the average of the Hoftyzer/Van Krevelen and Hoy solubility parameters.

[c] PVP/VA 60/40 (S-630).

Table 2
DSC data of drugs and excipients (heating rate 10 K min^{-1})

Compound	Melting endotherm onset (°C)	Heat of fusion (ΔH, J g^{-1})	T_g (°C)
Indomethacin	159.4	110.3	43.7
Lacidipine	182.1	100.9	48.0
PEG 8	57.8	189.6	−55
PEG 10	56.4	183.8	−50
PVP 12	–	–	114.0
PVP 30	–	–	164.2
PVP/VA	–	–	106.2
PVA	173.0	11.3	85
Citric acid	155.6	210.0	21.3
Lactose	229.6	Degrades	14.6
Mannitol[a]	166.1	328.7	12.6
Glucose	152.0	200.6	30.2
Sucrose	189.3	132.8	70.7

($n = 3$ For drug and $n = 2$ for excipient). Note, PVP, PVP/VA are amorphous polymers.
[a] Mannitol recrystallises on cooling of the melt, therefore, the T_g value estimated by Yu et al. (1998) is used.

For 'group 3' excipients minimal evidence for miscibility of drugs with excipients was found with thermal analysis. In the DSC thermograms two distinct melting endotherms, for drug and excipient at the expected T_{mo}, were detected (Fig. 2b and Table 3). Fig. 2b shows that a minimal increase in the heats of fusion for indomethacin and 'group 3' excipients was found, which may be evidence of some miscibility. However, in the case of indomethacin/mannitol and indomethacin/sucrose the resolution of the respective melt endotherms was not complete.

For indomethacin/citric acid and indomethacin/glucose only one melt endotherm was visible at a DSC heating rate of 10 K min^{-1} due to overlapping melting events. Changing the DSC heating rate to 2 K min^{-1} separated the indomethacin/glucose melt endotherms, but did not resolve the melts of indomethacin and citric acid. HSM of indomethacin and lacidipine/citric acid did not show any sign of miscibility (data not shown). For lacidipine/citric acid the T_{mo} could not be determined due to citric acid decomposition, which begins around 165 °C (Ford, 1986). TGA demonstrated a weight loss starting at 160 °C related to decomposition (data not shown).

For indomethacin/PVA, there was a significant decrease (Δ 8.4 °C) in the T_{mo} and a slight decrease in the heat of fusion at a (1:4) mass ratio (Δ 6.8 J g^{-1}). HSM analysis of indomethacin/PVA showed miscibility of indomethacin with amorphous regions of PVA. Crystalline PVA did not melt until around 200 °C and was not soluble in the molten indomethacin.

In general, thermal analysis supported the predictions from δ calculations. 'Group 1' excipients with a $\Delta\delta < 2$ $MPa^{1/2}$ exhibited miscibility with both drugs indicated by changes in the drug T_{mo} and visual evidence of miscibility with HSM. The excipients in 'group 3', with $\Delta\delta > 10$ $MPa^{1/2}$, showed small changes in the drug melt heat of fusion, but the drug T_{mo} remained virtually unchanged and HSM did not show evidence for miscibility. For indomethacin/PVA the $\Delta\delta$ is 8.9 suggesting limited miscibility based on the classification of Greenhalgh et al. (1999). DSC and HSM investigations indicated some miscibility between the compounds. For indomethacin/citric acid the $\Delta\delta$ is 5.6, suggesting miscibility, but this was not evident in experimental investigations. A miscible glass solution, however, has been reported for indomethacin/citric acid up to weight fraction of 0.25 citric acid (Lu and Zografi, 1998).

3.3. Thermal analysis of the glass transition

An amorphous solution will only be in the glassy state at a storage temperature below the T_g.

At storage temperatures above the T_g a less viscous, rubbery state will form, with an increased tendency to recrystallise (Lu and Zografi, 1998). The T_g of an amorphous solution will depend on both the drug and excipient T_g values and, therefore, a single T_g at a temperature between the T_g values of both components is evidence for formation of a miscible system. Partial miscibility is evident when the T_g of the drug is shifted towards the T_g of the excipient, or vice-versa.

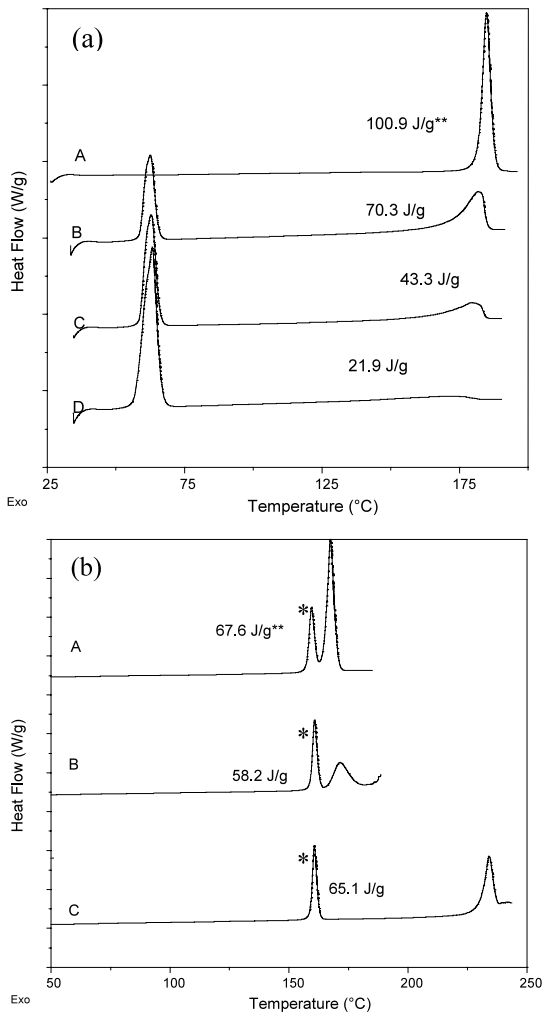


Fig. 2. DSC thermograms of drug and drug excipient mixtures. **, Heat of fusion for drug melts (ΔH). Expected ΔH (J g^{-1}) of drug based on dilution with excipient:lacidipine (4:1) 80.7, (1:1) 50.5, (1:4) 20.2. Indomethacin (1:1) 55.2. (a) Lacidipine/PEG 10, (A) lacidipine drug substance; (B) lacidipine/PEG (4:1); (C) lacidipine/PEG (1:1); (D) lacidipine/PEG (1:4). (b) Indomethacin, *, indomethacin melt; (A) indomethacin/mannitol (1:1); (B) indomethacin/sucrose (1:1); (C) indomethacin/lactose (1:1).

The T_g values of the individual drugs and excipients are shown in Table 2. The T_g values of drug/excipient quench cooled melts were determined for all 'group 1' excipients, mannitol and sucrose ('group 3') and both PVA and citric acid ('groups 2 and 3'). Table 4 shows the T_g values determined experimentally for both indomethacin and lacidipine/excipient blends.

In general, for 'group 1' excipients a single T_g at an intermediate temperature between the drug and the excipient T_g values was found. This supports the prediction from δ calculation and thermal analysis that these excipients are miscible with both drugs and, therefore, are likely to form an amorphous solid solution when melt extruded.

The T_g values of the drug/PEG melts were well below 25 °C and, therefore, an amorphous solution formed with these excipients will be in the rubbery state, prone to recrystallise and difficult to process. In the case of lacidipine/PEG 1:4 the T_g could not be detected as it may have been below the lowest temperature reached during the experiments (-35 °C).

Drug/PVP 12 and drug/PVP/VA melts had a single T_g value well above normal storage temperature (25 °C) and consequently glass solution formation is likely when the components are melt extruded. However, not all the T_g values are 50 °C above the storage temperature, and as detailed by Hancock and Zografi (1997) this suggests that there may be issues with the physical stability of these drug/excipient blends on long-term storage. Thermograms of both indomethacin/PVP 12 (1:1) and indomethacin/PVP/VA (1:1) melts are shown in Fig. 4A and B. Drug/PVP 30 (1:1 and 4:1) melts also exhibited a single T_g, at an appropriate temperature for storage. However, at a (1:4) mass ratio two T_g values were visible for indomethacin and lacidipine, one at an intermediate temperature and the other close to the T_g of PVP 30 (Fig. 4C shows lacidipine/PVP 30 melt as an example). As PVP 30 is a high molecular weight polymer this is probably due to the increased viscosity of the plasticised

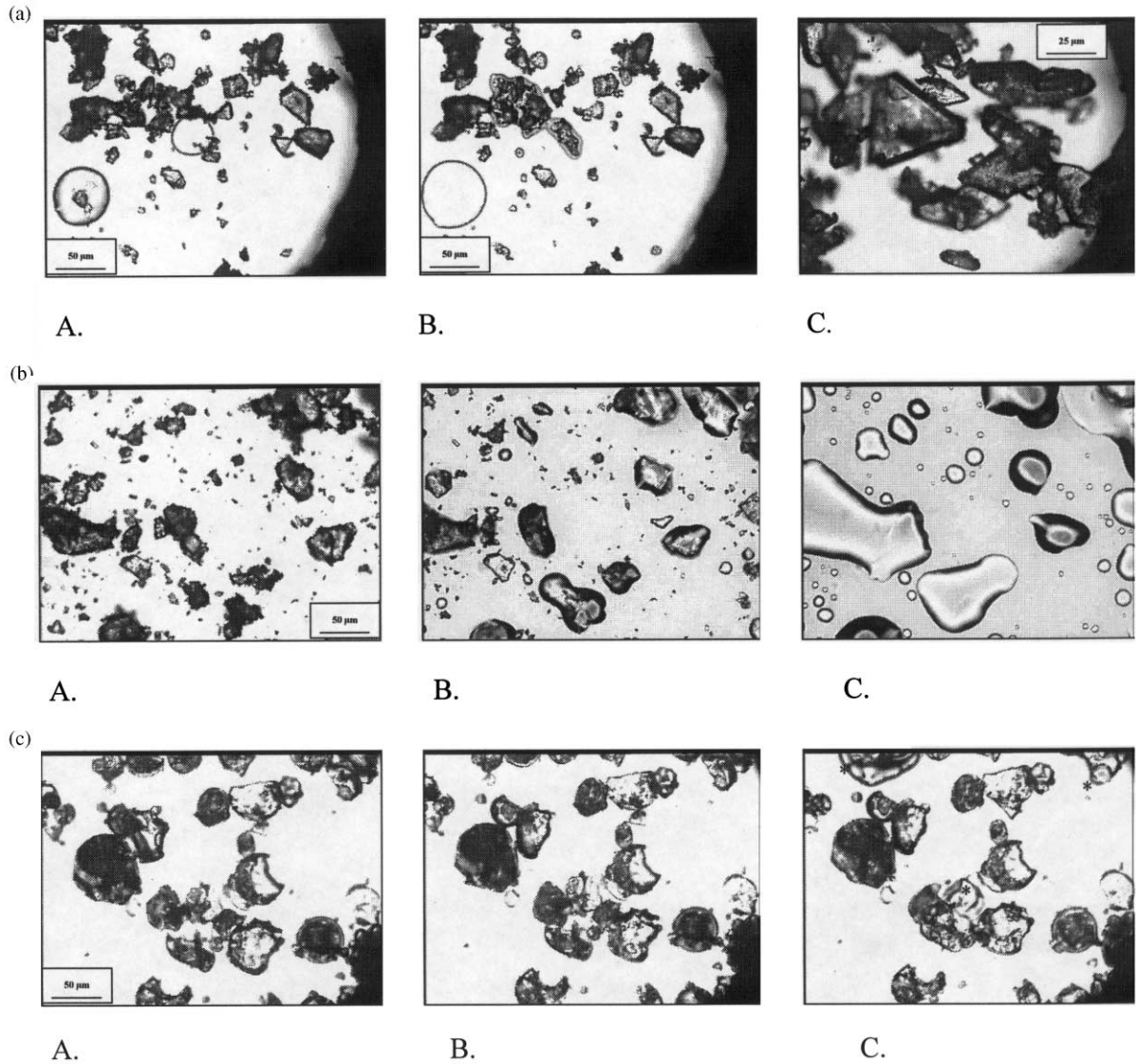


Fig. 3. (a) HSM of lacidipine and lacidipine/PEG 10 (1:1), (A) lacidipine/PEG 145 °C; (B) lacidipine/PEG 169 °C; (C) lacidipine 180 °C. (b) HSM of indomethacin/PVP/VA (1:1), (A) indomethacin/PVP/VA ambient; (B) indomethacin/PVP/VA 148 °C; (C) indomethacin/PVP/VA 164 °C. (c) HSM of lacidipine/PVP 30 (1:1), (A) lacidipine/PVP 30 ambient; (B) lacidipine/PVP 30 125 °C; (C) lacidipine/PVP 30 180 °C; *, regions of PVP dissolution.

polymer. High polymer viscosity has been previously reported to limit the miscibility of nifedipine and HPMC in DSC studies (Suzuki and Sunada, 1998).

Drug/mannitol melts (1:1) had an experimental T_g close to the temperature of drug alone. This is due to the recrystallisation of mannitol. In Fig. 5A it can be seen that mannitol forms a crystalline inclusion within the lacidipine glass following melting and quench cooling in the DSC. Lacidipine/sucrose melts exhibited two distinct T_g values at all mass ratios. Fig. 4D shows the T_g values of a lacidipine/sucrose (1:1) melt. As the temperature of both the T_g values remains practically un-

changed at all mass ratios this is strong evidence of an immiscible amorphous mixture (Yu et al., 1998) and confirms the lack of miscibility predicted by δ calculation and thermal analysis. Indomethacin/sucrose melts exhibited a single T_g, which was below the T_g of either component at a similar temperature for all mass ratios. From δ calculation ($\Delta\delta$ 12.7 $MPa^{1/2}$) and thermal analysis an immiscible system was predicted. Further investigation is required to explain the finding, but a similar result has been previously reported by Raudonus et al. (2000) for isomalt/sucrose melts.

Indomethacin/PVA melts exhibited a single experimental T_g, but also an endotherm at $\sim$ 187 °C, due to melting of PVA (data not shown). These results support the HSM finding that indomethacin is only miscible with the amorphous PVA phase. Lacidipine/PVA melts exhibited two

Table 3
Melt onset temperature (°C) for indomethacin/excipient and lacidipine/excipient mixes at various mass ratios

	Indomethacin			Lacidipine		
	1:4*	1:1	4:1	1:4	1:1	4:1
PEG 8	–[a]	101.5, 159.0[b]	144.6	–[a]	157.2	176.9
PEG 10	–[a]	106.1, 158.5[b]	146.9	124.2	166.8	171.7
PVP 12	122.5	126.5	151.8	169.3	166.3	174.8
PVP 30	–[c]	140.4	155.3	179.6	179.5	181.0
PVP/VA	–[c]	134.0	156.4	176.3	178.7	179.8
PVA	151.0	154.5	157.9	181.2	182.4	181.3
Citric Acid	_[d]	_[d]	_[d]	_[e]	_[e]	_[e]
Glucose[f]	156.2	155.7	155.8	179.9	179.8	180.0
Lactose	159.2	159.1	159.0	181.1	181.4	181.6
Mannitol	157.2	157.4	157.8	181.4	181.2	181.2
Sucrose	159.0	159.1	159.1	183.6	183.3	183.6

($n = 3$). *, 1:4 Corresponds to a drug:excipient mass ratio.
[a] Not detectable.
[b] Two distinct fusion events.
[c] Not detected due to dehydration of polymer.
[d] Not determined as melting endotherms overlap.
[e] Decomposition of citric acid interferes with lacidipine melt endotherm.
[f] DSC heating rate was 2 K min^{-1}.

Table 4
Glass transition temperatures (°C) of drug/excipient blends prepared by quench cooling the melt in a DSC

	Indomethacin			Lacidipine		
	1:4[a]	1:1	4:1	1:4	1:1	4:1
PEG 8	−12.1	−35.1	6.8	4.4	4.2	22.5
PEG 10	−10.0	−31.7	8.6	–	−9.8	9.1
PVP 12	84.2	68.8	49.8	92.2	76.2	54.8
PVP 30	84.9/163.0	71.7	72.9	86.4/161.1	64.8	54.3
PVP/VA	87.1	67.0	50.1	100.4	73.3	59.3
PVA	66.5	52.7	46.6	70.1/49.8	70.5/49.1	69.8/47.6
Citric acid	19.7/12.3	31.7/16.9	35.3/15.2	Degrades		
Mannitol		45.6			50.5	
Sucrose	38.0	38.0	39.4	68.9/50.5	70.7/49.5	71.4/49.9

[a] 1:4 Corresponds to a drug:excipient mass ratio.

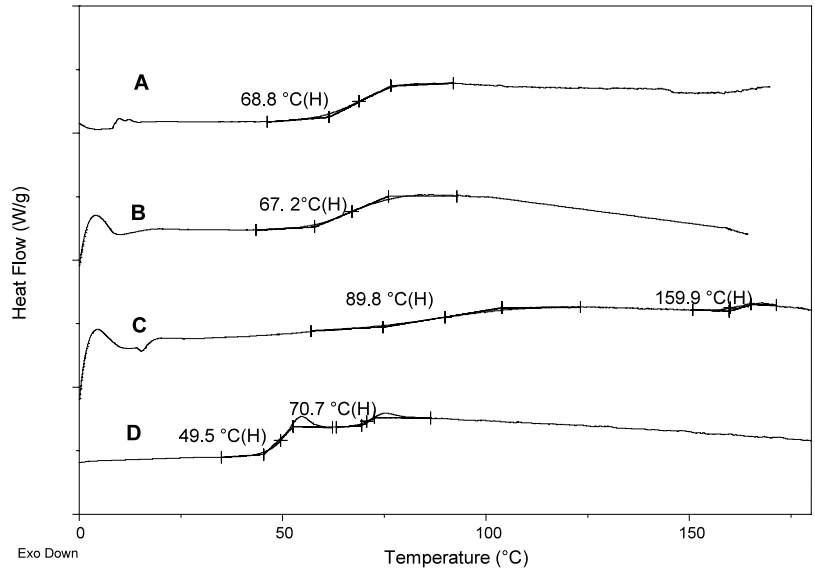


Fig. 4. T_g determination of quench cooled drug/excipient melts by DSC. (A) Indomethacin/PVP 12 (1:1); (B) indomethacin/PVP/VA (1:1); (C) lacidipine/PVP 30 (1:4); (D) lacidipine/sucrose (1:1).

T_g values similar to the respective T_g of each component confirming the lack of miscibility of the two compounds. Indomethacin/citric acid melts showed two T_g values and changing the mass ratio of drug to excipient led to significant changes in the T_g values. This indicates a degree of plasticisation by citric acid and that the components are partially miscible.

3.4. Melt extrusion

Due to the large quantities of drug substance required for melt extrusion not all drug/excipient blends were melt extruded.

Melt extrusion of indomethacin/PVP 30 (1:1 and 4:1), indomethacin/PVP/VA (1:1), lacidipine/PVP 30 (1:1) and lacidipine/PVP/VA (1:1) produced transparent and brittle solids typical of a glass solution (Fig. 5B shows lacidipine/PVP 30 (1:1) as an example). XRPD of the milled drug/PVP 30 (1:1 and 4:1) and drug/PVP/VA (1:1) extrudates showed an amorphous pattern, and SEM demonstrated a uniform morphology consistent with glass solution formation (Fig. 5D). Single T_g values well above the storage temperature were seen for both drugs when extruded with PVP 30 and PVP/VA (Table 5). These results for 'group 1' excipients support the prediction of a miscible glass solution from comparison of the calculated δ, thermal analysis of miscibility using DSC/HSM and T_g analysis. A summary of these findings is shown in Table 6. Lacidipine/PVP 30 (1:4) was not successfully melt extruded at 175 °C as the shear pins of the extruder broke, indicating high strain on the extruder. Increasing the temperature of the extruder up to 200 °C led to degradation. This anomaly was predictable from DSC/HSM and T_g analysis, but not from δ comparison, which does not account for the viscosity of the components (Table 6).

In comparison, melt extrusion of lacidipine with a 'group 3' excipient, mannitol (1:1), produced an opaque solid with peaks apparent in the X-ray powder diffractograms due to recrystallised mannitol. SEM of the extrudate provided evidence of crystalline particles in the lacidipine/mannitol system (Fig. 5C). Lacidipine/mannitol extrudate exhibited a T_g similar to that of the drug, due to the recrystallisation of mannitol (Table 5). Therefore, extrusion of lacidipine and mannitol resulted in a two-phase dispersion, one phase of amorphous drug and the other phase of

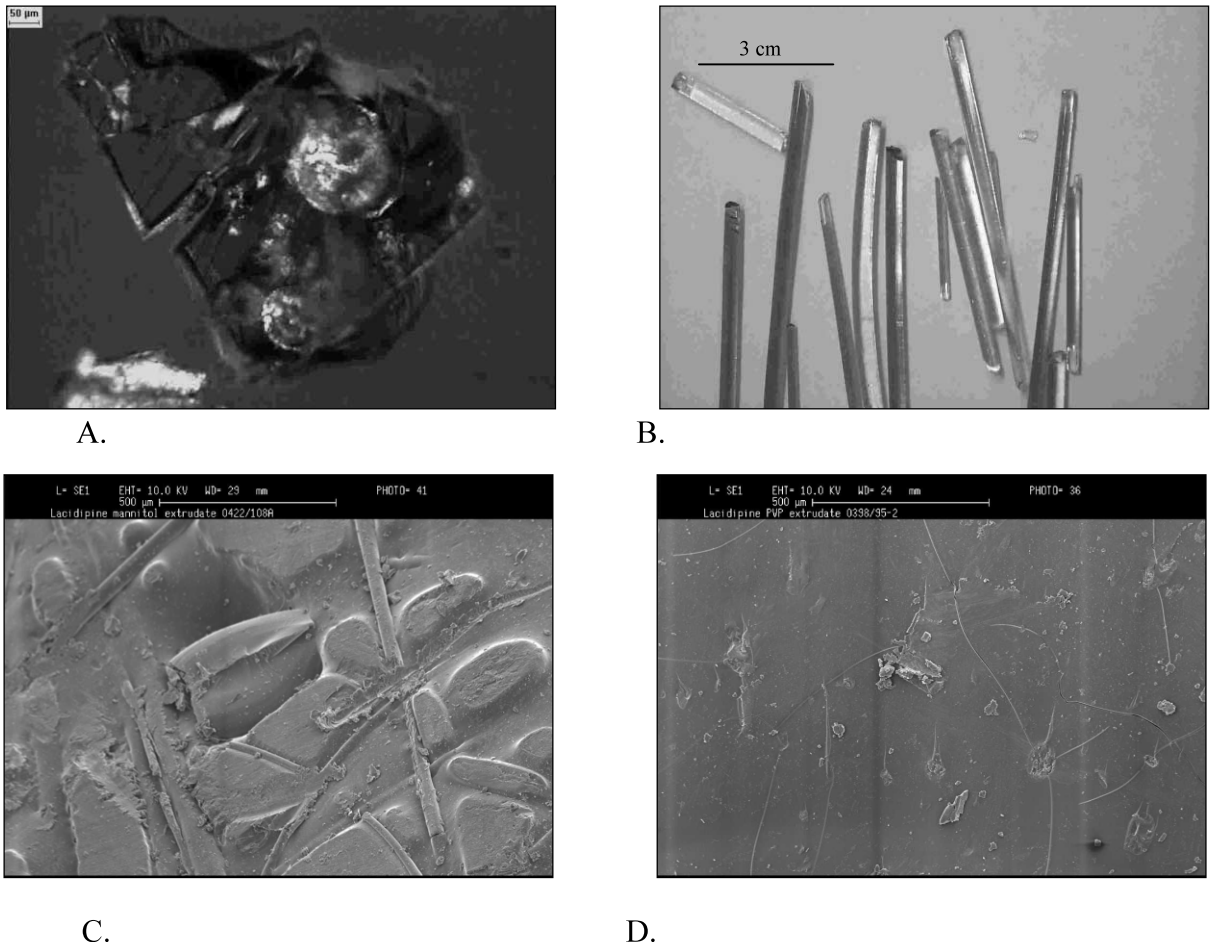


Fig. 5. Photograph and micrographs of lacidipine extrudates. (A) Polarised light microscopy of lacidipine/mannitol 1:1 quench cooled melt; (B) lacidipine/PVP 1:1 extrudate; (C) lacidipine/mannitol 1:1, intact; (D) lacidipine/PVP 1:1, intact.

Table 5
Glass transition (°C) of indomethacin and lacidipine melt extrudates

Drug	Excipient	Mass ratio	Water (% w/w)	T_g[a] extrudate (°C)
Indomethacin	PVP 30	1:1	1.7	76.1
		4:1	0.8	56.1
	PVP/VA	1:1	0.7	64.5
Lacidipine	PVP 30	1:1	2.5	78.4
	PVP/VA	1:1	0.5	75.6
	Mannitol	1:1	0.8	53.7

[a] Determined with MTDSC.

Table 6
Summary table of drug/excipient miscibility

Excipients	Group	Indomethacin					Lacidipine				
		$\delta_{\text{Hoftyzer/Hoy}}$	DSC melting	HSM	DSC T_g	Melt extrusion	$\delta_{\text{Hoftyzer/Hoy}}$	DSC melting	HSM	DSC T_g	Melt extrusion
PEG 8	1	+	+	+	+		+	+		+	
PEG 10	1	+	+		+		+	+	+	+	
PVP 12	1	+	+	+	+		+	+		+	
PVP 30	1	+	+		+/−[a]	+[b]	+	−	+	+/−[a]	+/−[b]
PVP/VA	1	+	+	+	+	+	+	+	+	+	+
PVA	2/3	[c]	+	+/−[d]	+		−	−	−	−	
Citric acid	2	[c]	[e]	−	−		[c]	Degrades			
Glucose	3	−	−				−	−	−		
Lactose	3	−	−				−	−			
Mannitol	3	−	−		−		−	−		−	−
Sucrose	3	−	−	−	−		−	−		−	

+, Miscible, as indicated by a change in the onset of drug melting (DSC melting), observed with HSM, a single T_g for quench cooled drug/excipient blends or melt extrudates (DSC T_g). −, Immiscible.

[a] Miscible at a drug/PVP 30 ratio of 1:1 and 4:1, immiscible at 1:4.

[b] A miscible glass solution was formed at a drug/PVP 30 ratio of 1:1 and 4:1 (indomethacin only), but not at 1:4 (lacidipine only).

[c] Cannot be predicted from δ calculation.

[d] Only miscible with amorphous PVA.

[e] Melting endotherms could not be resolved by DSC.

crystalline excipient, supporting the prediction from comparison of δ and thermal analysis of miscibility using DSC and HSM (Table 6).

Overlapping melts complicated predictions of the miscibility of indomethacin and citric acid. The fact that two T_g values were present at all mass ratios for quenched cooled indomethacin/citric acid blends indicated, at best, limited miscibility and not formation of an amorphous solid solution. Additionally, the low T_g values of the quenched cooled melts would indicate potential problems with stability and handling. In the case of lacidipine, citric acid was not a suitable candidate due to degradation.

The difficulty in determining the solubility behaviour of PVA could be related to its partially crystalline nature. Crystalline polymers are well known to be relatively insoluble and often only dissolve other components at their melting point (Van Krevelen, 1990). Indomethacin was found to be miscible with the amorphous component of PVA, but not with the crystalline component. The presence of crystalline material in the dispersion prevents solid solution formation and may affect physical stability of the amorphous component and, therefore, PVA is not a suitable melt extrusion candidate for indomethacin.

4. Conclusion

The selection of excipients for melt extrusion with a specific drug can be based on the difference between the calculated solubility parameters of drug and excipient. When the difference between drug and excipient solubility parameters is < 2.0 $MPa^{1/2}$, ('group 1') a glass solution is likely to result when the components are melt extruded. However, it must be borne in mind that the viscosity of the excipient may limit the drug/excipient ratio that can be extruded and, therefore, even for 'group 1' excipients further analysis using thermal methods should be undertaken before the drug and excipient are melt extruded. When the difference between drug and excipient solubility parameters is > 10 $MPa^{1/2}$ ('group 3') it is unlikely that a glass solution will be formed with melt extrusion. When the difference in solubility parameters is between 5–10 $MPa^{1/2}$ ('group 2'), prediction of glass solution formation is not possible, unless further investigation is performed with thermal analysis. However, DSC analysis of onset of drug melting was found to have limitations in assessing miscibility when both the drug and the excipient melt at similar temperatures. T_g analysis from DSC prepared quench cooled melts of drug and excipient provided an alternative means of predicting miscibility. Additionally, DSC T_g analysis indicated whether a glass solution formed with a specific drug and excipient for a given mass ratio would have a T_g above the storage temperature, which is important for physical stability.

Further studies are required to assess if this approach of combining the calculation of solubility parameter with thermal analysis to select suitable combinations of drug and excipient for glass solution formation by melt extrusion is applicable to a wider range of drugs and excipients.

Acknowledgements

The support of the Vernon Tews GlaxoWellcome Pharmacy Postgraduate Educational Fund for AF is gratefully acknowledged.

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