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RESEARCH PAPER

The Potential of Small-Scale Fusion Experiments and the Gordon-Taylor Equation to Predict the Suitability of Drug/Polymer Blends for Melt Extrusion

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ABSTRACT

The aim of this study was to investigate the use of small-scale fusion experiments and the Gordon-Taylor (GT) equation to predict whether melt extrusion of a drug with an amorphous polymer produces a stable amorphous dispersion with increased drug dissolution. Indomethacin, lacidipine, nifedipine, piroxicam, and tolbutamide were used as poorly soluble drugs. Drug/polyvinylpyrrolidone (PVP) blends were prepared at a 1:1 mass ratio. Small-scale fusion experiments were performed in a differential scanning calorimeter (DSC) and in stainless steel beakers. Extrusion was performed in a Brabender Plasti-corder. The glass transition temperatures T_g *were determined by DSC. Taking an average* T_g *from the DSC melt, beaker melt, and GT equation accurately predicted the extrudate* T_g*. Physical stability of beaker melt and extrudate samples was tested by X-ray powder diffraction (XRPD) and DSC after storage at 30°C (beaker melt) or 25°C (extrudate) and less than 10%, 60%, and 75% relative humidity (RH). Beaker melts were amorphous, apart from some residual crystallinity. Extrudates were amorphous after preparation. Except for indomethacin/PVP, which remained amorphous, the crystallinity of beaker melts and extrudates increased only at 75% RH. Recrystallization occurred even when the* T_g *of the sample was well above the storage temperature. Chemical stability of the beaker melts and extrudates was tested by capillary electrophoresis and high-performance liquid chromatography (HPLC). Stability was slightly improved in the extrudate compared to the beaker melt. In general, the order for rate of dissolution was crystalline drug was less than the physical mixture, which was less than the drug/PVP beaker melt, which was approximately equal to the extrudate. The use*

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of beaker melts allows a conservative estimate of the potential to melt extrude a drug. To predict physical stability, analysis of the T_g *must be combined with physical stability experiments.*

Key Words: *Drug/polymer blends; Gordon-Taylor equation; Melt extrusion; Solid dispersions.*

INTRODUCTION

Melt extrusion is currently being investigated for application in dosage form development in the pharmaceutical industry (1–3). During melt extrusion, drug is incorporated into excipient(s) by melting or plasticizing both the drug and excipient(s) using either one or two screws inside a heated barrel (2). The molten material is then cooled, typically on a chilled stainless steel conveyer belt. This approach may lead to the formation of a solid dispersion of drug in an excipient matrix, in which the drug is dispersed as a crystalline phase or as a solid solution. An amorphous solid solution is likely to exhibit an increased dissolution rate and potentially higher bioavailability of the drug (4,5).

The major advantages melt extrusion has over other solvent-based solid dispersion formulation techniques are that it is potentially cheaper and more environmentally friendly (1). However, pilot plant extruders use a considerable quantity of drug, which is not often available at an early development stage. Therefore, small-scale predictive techniques are required to select potential drug candidates successfully for melt extrusion.

For a drug/polymer blend to be suitable for extrusion, the resulting product must be physically and chemically stable, and the drug must show an increase in dissolution compared to crystalline drug and a drug/polymer physical mixture. Amorphous formulations are metastable, and poor physical stability is the major factor in preventing more frequent application of amorphous formulations in drug delivery (6). Therefore, for drug candidate selection to be successful, any smallscale technique must be able to give an indication of the physical stability of the amorphous extrudate. The glass transition temperature T_g is often used to estimate the physical stability of an amorphous system and, for a given temperature, indicates whether the amorphous formulation is in a glassy or a rubbery state (4,5,7,8). The glassy state has greater physical stability, being less prone to recrystallization, and is easier to process than the rubbery state (9). The T_g of a drug can be determined experimentally using differential scanning calorimetry (DSC), or it can be estimated from the melting point T_m based on the empirical relationship $T_g \approx 0.7\ T_m(\mathrm{K})$ (10). T_g prediction for a drug/polymer blend can be performed using the Gordon-Taylor (GT) equation (5):

$$T_{g_{mix}} = \frac{w_1 \cdot T_{g_1} + K \cdot w_2 \cdot T_{g_2}}{w_1 + K \cdot w_2} \qquad K = \frac{T_{g_1} \cdot \rho_1}{T_{g_2} \cdot \rho_2} \quad (1)$$

where T_g is the glass transition temperature, w_1 and w_2 are the weight fractions of the components, and K is calculated from the densities ρ and T_g of the amorphous components. However, no information regarding chemical stability or increase in dissolution of the melt extrudate can be derived based on analysis of the T_g alone.

This article reports on the use of small-scale fusion experiments and the limitations of the Gordon-Taylor equation to predict the suitability of drug compounds for melt extrusion based on physical stability, chemical stability, and dissolution. Fusion experiments were performed both in a DSC and in stainless steel beakers, the latter yielding sufficient material for physical and chemical stability testing and dissolution experiments. Polyvinylpyrrolidone (PVP) was used as a model polymer in this study. PVP, a highly water-soluble, amorphous extrusion excipient, can enhance the wetting of the dispersed drug (11) and improve the physical stability of the amorphous dispersion (12–14).

EXPERIMENTAL

Materials

Indomethacin, lacidipine, nifedipine, piroxicam, and tolbutamide all show dissolution-rate-limited low oral bioavailability in the crystalline state and have melting points below 210°C (onset for decomposition of PVP). Indomethacin, nifedipine, piroxicam, and tolbutamide were purchased from Sigma Aldrich (Dorset, UK). Lacidipine and PVP (k30) were supplied by GlaxoWellcome (Ware, UK). Lacidipine and nifedipine samples were protected from light at all times.

Preparation of Solid Dispersions by Differential Scanning Calorimetry

Pure drugs and drug/PVP blends (5–10 mg) were melted in a TA Instruments 2920 DSC (Surrey, UK) at

10 K min^{-1} with a nitrogen purge at 20 ml min^{-1} using crimped aluminum pans with a pierced lid. Cooling of melts was achieved by placing a stainless steel jacket containing liquid nitrogen over the cell (''quench cooling''). Drug/PVP blends at a 1:1 weight ratio were prepared by lightly grinding accurately weighed quantities of drug and PVP in a mortar for 2 min.

Preparation of Solid Dispersions by Beaker Melt

Production of 10 g melts was accomplished by heating drug/PVP blends in a stainless steel beaker (200 ml) using a hot plate with thermostat. Target melting temperatures for the drug were obtained from DSC analysis, and rapid cooling of the sample was achieved by partially submerging the beaker in ice-cold water. Samples were stored at −20°C in sealed amber glass jars with desiccant. Samples for characterization and stability testing were lightly ground with a mortar and pestle after manufacture. The 25–250 μm particle size fraction was placed on stability at 30°C/<10% relative humidity (RH; desiccator over silica gel), 30°C/60% RH (saturated solution of $NaBr \cdot 2H_2O$), and in an incubator at 30°C/75% RH.

Preparation of Solid Dispersions by Melt Extrusion

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 temperature of melt extrusion was approximated as follows based on the results of the DSC and beaker melt preparation methods: indomethacin 165°C, lacidipine 180°C, nifedipine 165°C, piroxicam 198°C, and tolbutamide 120°C. However, it must be remembered that the actual temperature of the material in the extruder may be higher than that indicated by the temperature settings due to localized heating caused by the input of mechanical energy from the screws. Therefore, melt extrusion could potentially be performed at temperatures lower than predicted by DSC melts and beaker melts.

The heating barrel of the extruder 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 machine. Zones 2 to 4 were kept at a constant temperature for each drug/PVP blend, as described above. The powder blends were manually fed into the melt extruder. The screw speed was adjusted to 20–30 rpm, resulting in a residence time in the barrel of approximately 2 to 3 min for the drug/PVP blends. The extrudate was air cooled on a conveyer belt. Extrudate was stored in sealed bags with desiccant (silica gel) at less than 25°C.

The extrudate was milled in a Glen Creston (Middlesex, UK) DFH48LL hammer mill with a 0.5-mm screen. A particle size range of 25 to 250 μm was selected for analysis and was placed on stability at 25°C/<10% RH, 25°C/60% RH, and 25°C/75% RH.

Thermal Analysis

Samples were heated in a TA Instruments 2920 DSC at 10 K min^{-1} with a nitrogen purge at 20 ml min^{-1} using crimped aluminum pans. Samples that showed a recrystallization exotherm on heating were analyzed further by controlled cooling at 10 K min^{-1} using a liquid nitrogen cooling accessory (LNCA). Sample analysis was performed in duplicate.

Modulated temperature DSC (MTDSC) was performed using the TA Instruments 2920 with LNCA. Samples (5–10 mg) were sealed in aluminum pans. 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. MTDSC was used if absorbed water made accurate determination of the T_g with conventional DSC difficult.

Thermal decomposition of the drugs was investigated by thermogravimetry using a TA Instruments 2950 analyzer at a heating rate of 10 K min^{-1} and a nitrogen flow of 100 ml min^{-1}. Duplicate samples (20–30 mg) were heated until weight loss was detected.

X-ray Powder Diffraction

X-ray powder diffraction (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 nickel-filtered CuK_α radiation (30 kV and 40 mA). Samples were prepared as either backfilled samples (~300 mg sample size) or as front-filled recessed silica wafer samples (~100 mg sample size).

Scans with a 0.01° 2θ step size and 20 s per step were used to assess quantitatively the peak area of indomethacin (21.2°–22.2° 2θ), lacidipine (21.5°–23° 2θ), nifedipine (14.0°–15.5° 2θ), and tolbutamide (11.5°–14.0° 2θ). Physical blends of drug in PVP were used to calibrate the XRPD on the day of the experiment, and peak areas were obtained by analysis using the Philips APDW

software. The limit of detection was approximately 1% crystalline drug.

Density

Density measurements of amorphous drugs and PVP were performed using a nitrogen pycnometer (AccuPye 1330, Micromeritics, Norcross, GA) with a cell size of 1.0 cm^3. Measurements were performed in triplicate using ground beaker melt samples with a sample size of 0.25–0.35 g.

Moisture Content

Moisture content was determined by both thermogravimetry and Karl Fischer analysis (Turbo2 blending, Karl Fischer, Orion, UK). Moisture content was determined in duplicate for both techniques.

Chemical Stability

Capillary electrophoresis (CE) and HPLC were used to assess the chemical stability of beaker melt samples and extrudates. The CE system consisted of a P/ACE 5500 CE (Fullerton, CA) and a fused silica column (27 cm, 50 μm id, Composite Metals, Hallow, UK). A voltage of 11 kV was applied. On-line measurements were performed at 40°C with ultraviolet (UV) detection at 210 nm (Hewlett Packard, Bracknell, UK) (15). Accurately weighed drug samples for analysis were dissolved in a microemulsion (16) at a concentration of approximately 1 mg ml^{-1}. PVP did not interfere with the analysis as it was rapidly eluted from the column due to its high water solubility.

The HPLC system consisted of a HP 1090 liquid chromatograph (Hewlett Packard, Bracknell, UK) and an Inertsil (G. L. Sciences, Tokyo, Japan) ODS-2 column (5 μm 4.6 × 150 mm) (Phenomonex, Cheshire, UK). On-line analysis was carried out at 210 nm using a Hewlett Packard 8453 diode array spectrophotometer (Bracknell, UK) at 40°C, with 5 μl of a 1 mg ml^{-1} solution of drug injected onto the column. A gradient system of water (0.05% formic acid) and acetonitrile (0.05% formic acid) was used as the mobile phase.

For both systems, decomposition was based on the percentage decrease in the main drug peak from the expected value.

Dissolution

Dissolution was undertaken within 24 h of sample preparation using a USP 2 apparatus (37°C, 50 rpm) with UV analysis (Hewlett Packard 8453 diode array spectrophotometer). Either 500 ml or 900 ml media volume was used. The media was either pH 6.8 phosphate buffer (indomethacin and tolbutamide) or 1% sodium dodecyl sulfate (SDS) in water (lacidipine, nifedipine, and piroxicam). The pH of the SDS media was constant (6.4) throughout the 60-min experiment. A UV wavelength specific for each compound and free from interference with the PVP spectrum was selected. Measurements were performed in triplicate.

Scanning Electron Microscopy

Samples were coated with a thin gold-palladium layer by sputter coating (Bio-rad E5100, Microscience Division, Hemel Hempstead, UK). The samples were investigated with a Cambridge S360 scanning electron microscope (SEM; Cambridge, UK), which was operated with an acceleration voltage of 10 kV.

RESULTS

Sample Preparation by Differential Scanning Calorimetry

Drug Melt

On reheating of the quench-cooled samples, indomethacin (not shown) and lacidipine (Fig. 1a) showed a T_g as the only thermal event. Nifedipine (Fig. 1b), piroxicam (Fig. 1c), and tolbutamide (Fig. 1d) exhibited a T_g followed by a recrystallization exotherm T_c and melting endotherm T_m. In both groups, the ratio of the T_g(K) to the melting temperature (K) was approximately 0.7 (Table 1), which is in agreement with a large range of low molecular weight pharmaceuticals investigated by Fukuoka et al. (10).

Enthalpies of recrystallization for nifedipine, piroxicam, and tolbutamide were lower than the corresponding enthalpies of melting (Table 1), indicating that some recrystallization might have occurred before reheating. This interpretation is supported by the detection of a recrystallization exotherm before the T_g when the melt was cooled at a controlled cooling rate (10 K min^{-1}; Fig. 1d shows the example of tolbutamide with a recrystallization exotherm onset of 75.2°C).

Piroxicam and tolbutamide showed differences in melting temperatures after recrystallization, suggesting that recrystallization to other polymorphic forms had occurred. Figure 1c shows that, following melting and quench cooling of piroxicam (T_m 205°C, polymorphic form I; 17), recrystallized drug (T_c 133°C) exhibited two

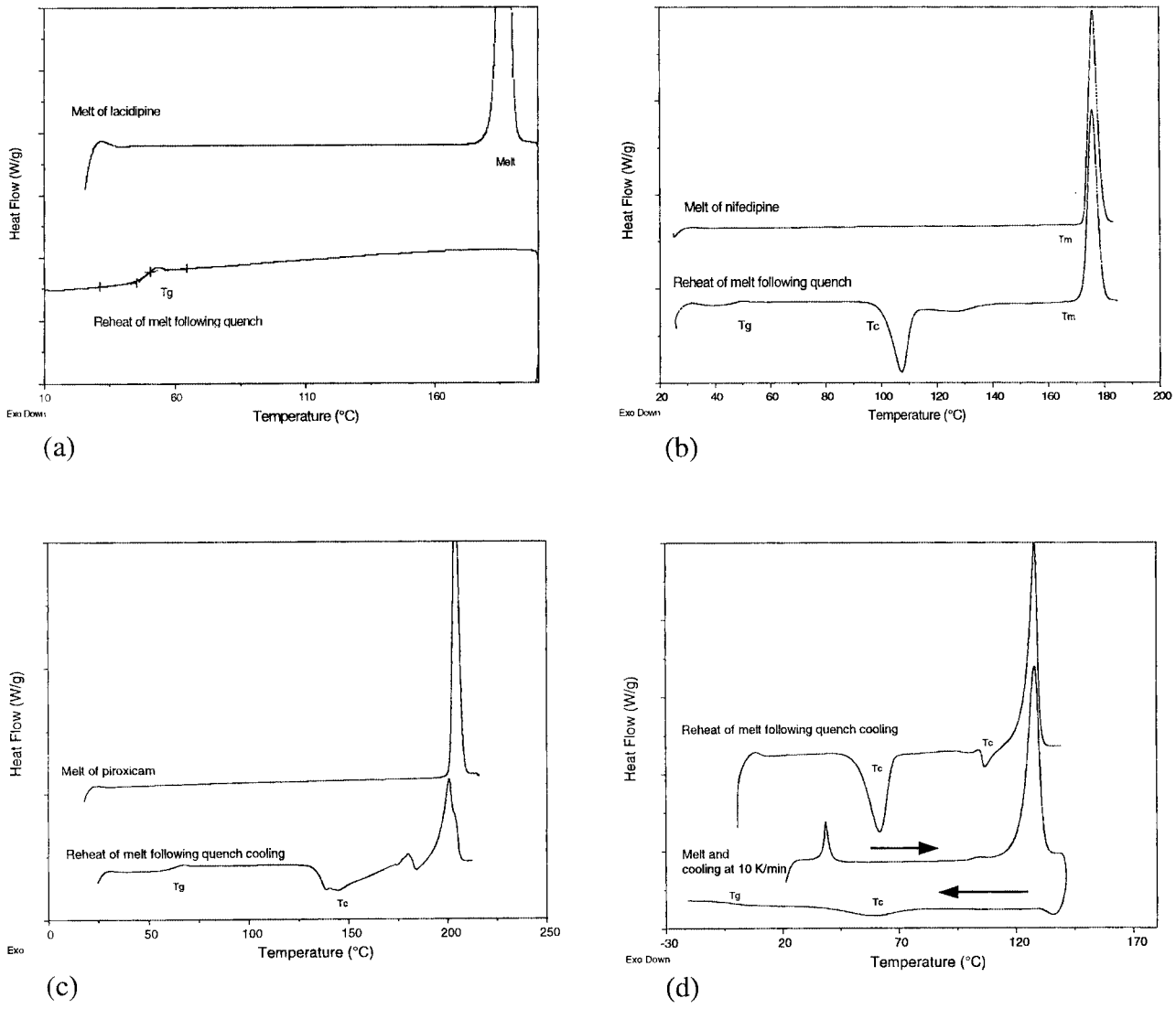


Figure 1. DSC thermograms of drug melts: (a) lacidipine melt and reheat of quench-cooled melt; (b) nifedipine melt and reheat of quench-cooled melt; (c) piroxicam melt and reheat of quench-cooled melt; (d) tolbutamide reheat of quench-cooled melt and controlled cooling at 10 K min^{-1} following melting.

endothermic transitions, at 180°C and 201°C, suggesting recrystallization of the melt to form III, followed by a transition to form II (17).

In the case of tolbutamide, the melting and reheating experiments were further complicated by the existence of three endothermic transitions in the melting thermogram (Fig. 1d). The endotherm at 39.6°C has been described previously as a solid-state transition (18). The small endotherm at 100°C can be attributed to a transition of form II to form I (19). The endotherm at 128°C is the melting temperature of form I. Figure 1d shows the recrystallized form, exhibiting one endotherm (128°C), preceded by two exotherms at 58°C and 105°C.

Table 1 shows the onset of degradation for the drugs determined by TGA. On heating, both lacidipine and piroxicam begin to degrade before melting. Indomethacin decomposes when melting, whereas tolbutamide and nifedipine do not begin to degrade until well above the T_m.

Drug/Polyvinylpyrrolidone Melt

A similar set of experiments as for the pure drugs was carried out for 1:1 drug/PVP blends (Table 2). In

Table 1

Differential Scanning Calorimetry/Thermogravimetric Analysis (DSC/TGA) Data for Pure Drugs

Compound	T_m (max) (°C)	Enthalpy Fusion (J/g)	T_c (max) (°C)	Enthalpy Recrystallization (J/g)	T_g Half-ht (°C)	T_g Onset (°C)	Ratio T_g/T_m [a]	TGA (°C) Degradation
Indomethacin	162.7 ± 1.4	109.6 ± 5.2	—	—	43.7 ± 0.1	42.2	0.73	>163
Lacidipine	184.8 ± 0.13	99.8 ± 4.2	—	—	48.0 ± 0.4	46.3 ± 1.2	0.70	>176
Nifedipine	175.2 ± 0.9	106.7 ± 4.2	107.0 ± 0.5	87.0 ± 2.1	46.7 ± 0.7	44.5 ± 0.5	0.71	>195
Piroxicam	204.9 ± 1.1	106.8 ± 1.7	140.1 ± 10.4	59.3 ± 2.8	62.2 ± 0.5	60.1 ± 1.3	0.70	>198
Tolbutamide	128.4 ± 0.3[b]	91.4 ± 3.0	60.7 ± 1.8	59.5 ± 5.5	2.9 ± 0.9	1.03 ± 1.2	0.69	>166
Polyvinylpyrrolidone	—		—	—	168	159.9	—	>210

$n = 2$.

[a] Ratio of T_g/T_m in K/K.

[b] Additional solid-state transition at 39.6°C.

all cases, the melting peak of the drug was shifted to a lower temperature compared to the pure drug and had an increased width of the melting endotherm. On reheating of the quench-cooled samples, the T_g was raised compared to that of the pure drugs. The quench-cooled melts of all samples did not show recrystallization or melting events.

TGA results indicated that both lacidipine and piroxicam/PVP blends began to degrade before drug melting (Table 2). The piroxicam/PVP mixture was charred when removed from the DSC cell. Indomethacin, nifedipine, and tolbutamide/PVP blends have drug melting points well below the onset of drug degradation.

Sample Preparation by Beaker Melt

Physical Stability of Beaker Melts

Table 3 summarizes the stability findings for drug/PVP beaker melts. In all cases, the cooled beaker melts of drug/PVP blends were opaque, brittle solids. Preparation of a piroxicam/PVP melt was not possible due to decomposition. Lacidipine and nifedipine/PVP beaker melts consistently exhibited low levels of crystallinity, termed *residual crystallinity*, on the day of preparation. The T_g of drug/PVP melts were determined with MTDSC due to the small amount of water taken up by the samples following preparation. Table 4 shows both the T_g and moisture contents of the drug/PVP beaker melts.

Indomethacin/PVP beaker melts were stable for 5 weeks. Tolbutamide/PVP beaker melts were also stable for 5 weeks, except at 30°C/75% RH, for which crystallinity was apparent after 1 week (forms I, II, and IV). XRPD demonstrated that the residual crystallinity of lacidipine and nifedipine/PVP beaker melts did not increase over 5 weeks at 30°C/<10% RH and 30°C/60% RH. An increase in peak area was noted for both melts at 30°C/75% RH.

Table 2

Differential Scanning Calorimetry/Thermogravimetric Analysis (DSC/TGA) Data of DSC Prepared Drug/Polypyrrolidone (PVP) Melts

Drug/PVP Blend	T_m (°C)	T_g Half-ht (°C)	T_g Onset (°C)	TGA (°C) Degradation
Indomethacin	151.1 ± 1.0	75.7 ± 0.3	67.1 ± 1.3	>190
Lacidipine	182.6 ± 0.1	84.2 ± 0.8	51.8 ± 1.0	>175
Nifedipine	171.2 ± 0.2	83.6 ± 1.0	71.6 ± 0.7	>172
Piroxicam	198.3 ± 0.5	85.9 ± 4.9	74.8 ± 4.8	>180
Tolbutamide	117.6 ± 3.0	28.6 ± 0.5	27.3 ± 0.5	>168

$n = 2$.

Table 3

X-Ray Powder Diffraction (XRPD) Data of Drug/Polyvinylpyrrolidone (PVP) Beaker Melts

	XRPD Stability			
Drug/PVP Blend	Day 1	5 Weeks, 30°C/<10% RH	5 Weeks, 30°C/60% RH	5 Weeks, 30°C/75% RH
Indomethacin	A	A	A	A
Lacidipine	A_{RC}(~4%)	A_{RC}(~4%)	A_{RC}(~4%)	C (>15%)
Nifedipine	A_{RC}(~7%)	A_{RC}(~7%)	A_{RC}(~7%)	C (>12%)
Piroxicam			Degrades	
Tolbutamide	A	A	A	C

A, no crystalline peaks detectable (amorphous); A_{RC}, amorphous with only residual crystallinity; C, crystalline peaks; RH, relative humidity.

Table 4

T_g *Values of Samples After Preparation (K)*

Drug/PVP Blend	DSC[a] T_g	GT[a]	T_g Expected/ Predicted	Beaker Melt T_g	% H_2O w/w	GT	T_g Expected/ Predicted	GT[b]	T_g[b] Expected/ Predicted	Extrusion T_g	% H_2O w/w	GT	T_g Expected/ Predicted
Indomethacin	349	374	0.93	331	2.5	355	0.93	—	—	352	1.7	360	0.98
Lacidipine	358	373	0.96	343	2.7	354	0.97	356	0.95	352	2.5	355	0.99
Nifedipine	357	376	0.95	339	2.3	357	0.95	362	0.94	354	1.9	361	0.98
Tolbutamide	302	342	0.88	303	2.2	329	0.92	—	—	312	1.61	333	0.94

The amorphous densities were indomethacin 1.34 g cm^{-3}, lacidipine 1.20 g cm^{-3}, nifedipine 1.36 g cm^{-3}, and tolbutamide 1.25 g cm^{-3}. Density of PVP was 1.16 g cm^{-3}.

DSC, differential scanning calorimetry; GT, Prediction of T_g based on expanded Gordon-Taylor equation (Eq. 2); PVP, polyvinylpyrrolidone.

[a] Without moisture (removed during DSC melt).

[b] Corrected for residual crystallinity.

Chemical Stability of Beaker Melts

The percentage decomposition of the drug/PVP melts is shown in Fig. 2. Piroxicam/PVP beaker melts were not tested for decomposition due to the sample being visibly degraded.

Dissolution of Beaker Melts

Drug/PVP melts have higher dissolution rates than the physical mixtures and the crystalline drugs, except for tolbutamide, for which no significant difference in dissolution was found for the physical mixture and drug/PVP melt (Table 5).

Extrusion

Indomethacin, lacidipine, and nifedipine/PVP blends resulted in transparent, yellow, brittle extrudates. However, tolbutamide/PVP produced an opaque, white solid,

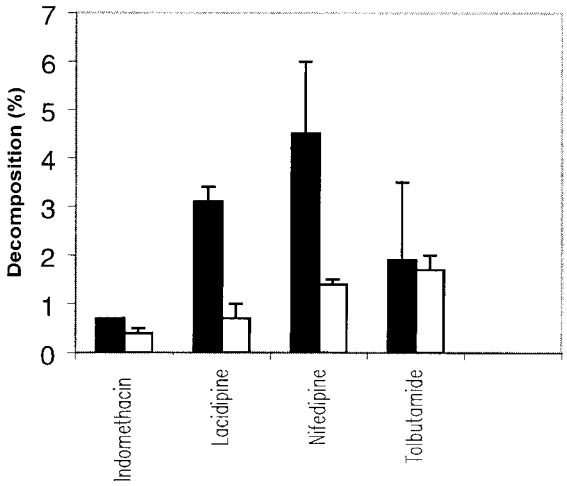


Figure 2. Chemical stability of beaker melts and extrudates: ■, drug/PVP melt, □, extrudate.

Table 5

Dissolution of Crystalline Drugs, Drug/Polyvinylpyrrolidone (PVP) Blends, and Extrudates as Percentage Drug Dissolved at 10 min (Q10) and 60 min (Q60)

									Extrudate Relative Dissolution Rate					
	Crystalline		Physical Mix		Drug/PVP Melt		Extrudate		Crystalline Drug		Physical Mix		Drug/PVP Beaker Melt	
	Q10	Q60	Q10	Q60	Q10	Q60	Q10	Q60	Q10	Q60	Q10	Q60	Q10	Q60
Indomethacin	27.3	40.9	40.2	56.0	99.8	99.2	101.9	99.2	3.7	2.4	2.5	1.8	1.0	1.0
Lacidipine	3.8	7.0	5.3	14.0	30.7	41.4	75.3	79.5	19.8	11.4	14.2	5.7	2.5	1.9
Nifedipine	16.4	21.5	34.8	34.7	39.3	49.3	35.6	50.1	2.2	2.3	1.0	1.4	0.9	1.0
Piroxicam	17.0	56.5	18.8	50.3	—	—	—	—	—	—	—	—	—	—
Tolbutamide	61.2	72.5	60.0	71.1	42.4	80.5	86.9	83.8	1.4	1.2	1.4	1.2	2.0	1.0

$n = 3$.

which was brittle after cooling. Piroxicam/PVP was not successfully extruded due to degradation. Tolbutamide/PVP extrudate was found to have a porous structure in the SEM, whereas all the other extrudates appeared as a uniform, solid phase (Fig. 3). The appearance of the tolbutamide/PVP extrudate may be due to the inclusion of vapor pockets in the matrix as a consequence of the lower extrusion temperature. Despite this, the water content of the tolbutamide extrudate was similar to that of the other extrudates (Table 4).

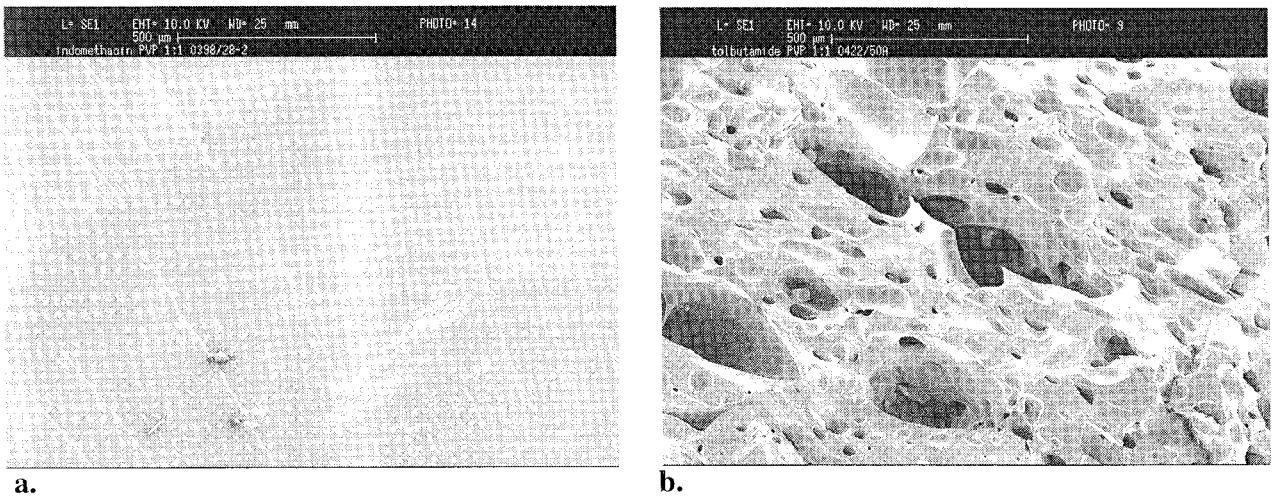
Extrudates were milled, sieved, and characterized by DSC, XRPD, and dissolution. XRPD analysis confirmed that recrystallization did not occur with milling. DSC analysis confirmed the XRPD findings as the thermograms only showed one T_g (Table 4), but no crystalline melt endotherm. Therefore, extrudates were classified as amorphous solid solutions.

Physical Stability of Extrudates

Extrudates were stable for 2 months at 25°C/<10% RH and 25°C/60% RH. At 25°C/75% RH, only indomethacin extrudate remained amorphous, whereas the other samples showed some degree of crystallinity in the XRPD (Table 6). The T_g's of the extrudates following 5 weeks of storage, determined by MTDSC, are also shown in Table 6.

Chemical Stability of Extrudates

The percentage decomposition values were as follows: indomethacin extrudate 0.41% ± 0.07%, lacidipine



a. **b.**

Figure 3. Scanning electron micrographs: (a) indomethacin/PVP extrudate; (b) tolbutamide/PVP extrudate.

Table 6

Physical Stability of Extrudates After 2 Months of Storage

	25°C/<10% RH			25°C/60% RH			25°C/75% RH		
	XRPD	T_g Onset (°C)	T_g Half-ht (°C)	XRPD	T_g Onset (°C)	T_g Half-ht (°C)	XRPD	T_g Onset (°C)	T_g Half-ht (°C)
Indomethacin	A	66.5	75.1	A	44.1	47.0	A	32.5	36.1
Lacidipine	A	72.6	84.5	A	46.5	48.8	C	15.5	20.0
Tolbutamide	A	39.0	45.5	A	5.8	11.8	C	0.5	4.4
Nifedipine	A	67.1	74.5	A	52.2	53.3	C	21.9	25.5

A, amorphous; C, crystalline peaks detectable ($n = 2$); RH, relative humidity; XPRD, X-ray powder diffraction.

0.73% ± 0.25%, nifedipine 1.4% ± 0.13%, and tolbutamide 1.7% ± 0.3% (Fig. 2).

Dissolution of Extrudates

The dissolution rates of all four drug/PVP extrudates were increased in comparison to crystalline drug substance and physical blends of drug and PVP (Table 5). Gains in comparison to drug/PVP beaker melts were not apparent for indomethacin, nifedipine, and tolbutamide at Q_{60}, but were significant for lacidipine and tolbutamide extrudate at Q_{10}.

The Gordon-Taylor Equation for T_g Prediction

For the drug/PVP beaker melts and extrudates, a ternary system is formed as water is also present. Any moisture in the sample must be included in the GT equation as water is a potent plasticizer and thus reduces the T_g. An expanded GT equation has been derived by Lu and Zografi (20) to predict the T_g for ternary systems:

$$T_{g_{mix}} = \frac{w_1 \cdot T_{g_1} + K_1 \cdot w_2 \cdot T_{g_2} + K_2 \cdot w_3 \cdot T_{g_3}}{w_1 + K_1 \cdot w_2 + K_2 \cdot w_3} \qquad (2)$$

$$K_1 = \frac{T_{g_1} \cdot \rho_1}{T_{g_2} \cdot \rho_2} \qquad K_2 = \frac{T_{g_1} \cdot \rho_1}{T_{g_3} \cdot \rho_3}$$

where ρ is the amorphous density, w is the weight fraction, and T_g is the experimental T_g. The T_g of water is 136 K (20) ρ of water is 1.0.

In Table 4, the experimentally determined values for T_g of the drug/PVP preparations are compared to those predicted by the GT equation. The predicted values are higher than the experimental values for all the preparation techniques. This is in agreement with previous findings, especially if drug and polymer are present in similar quantities (21). For both the lacidipine and nifedipine/PVP beaker melts, some crystallinity remained after preparation. This means that the amorphous system under investigation did not have a 1:1 ratio for GT equation prediction. Correcting for crystalline content leads to a further decrease in the ratio of experimental-to-predicted T_g.

DISCUSSION

Prediction of Physical Stability

The GT equation assumes ideal mixing of the components. A nonhomogeneous system caused by a lack of mixing or miscibility between drug and polymer will affect the experimental T_g value (22). The application and accuracy of the expanded GT equation for predicting the T_g of ternary mixtures has been investigated previously, with PVP, indomethacin, and citric acid (20). The authors concluded that the experimental T_g values were significantly lower than the predicted values, with T_g experimental/T_g predicted values averaging 0.94. Differences in the values were attributed to miscibility gaps.

The highest level of mixing occurs in melt extrusion due to the high degree of shear supplied by the counter-rotating, intermeshing twin-screw design and extrudate T_g values were closest to the GT values (Table 4). In the DSC system, there is no mixing, but the closed nature of the system and the small sample size ensures that thermal gradients are reduced, and dissolution of the PVP in the molten drug may readily occur. The beaker melt system incorporates limited mixing, but is an open system in which the temperature is harder to regulate, and thermal gradients are likely to occur; consequently, the values for T_g were furthest from the GT.

In the case of tolbutamide/PVP DSC melts, the T_g of the system was 40 K below that predicted by the GT equation. This very large discrepancy may be explained

by the low melting point of tolbutamide (127°C) compared to the softening point of PVP (168°C). At the melting temperature of the drug, the polymer may not have completely softened. Combined with the lack of mixing in the DSC, this may result in a nonhomogeneous system. In the beaker melt, the T_g was 26 K below the theoretical value, whereas in the extrudate, the discrepancy was reduced to 21 K.

Comparing the T_g values determined from DSC melts, beaker melts, and the GT equation to the actual extrudate T_g allows an assessment of the different approaches to predict T_g of the extrudate (Table 7). The GT equation overestimates the T_g of the extrudate, whereas the DSC melts and beaker melts both underestimate the T_g of the extrudate. Therefore, to arrive at the best prediction of the extrudate T_g, the three predictive values were averaged. The values given have a $T_{g_{combined}}/T_{g_{extrudate}}$ ratio of 1.00 (with residual moisture content included in the GT equation), allowing an accurate estimation of extrudate T_g.

Theoretically, the higher the T_g, the more physically stable the amorphous state, but deviations from this rule have been reported for pure drugs. For example, amorphous indomethacin and phenobarbital have an identical T_g, but phenobarbital is less stable (10). In the current study, piroxicam (pure drug) rapidly recrystallized on cooling of the DSC melt, even though its T_g was the highest of all the five drugs investigated (Table 1). Consequently, it has been suggested that amorphous materials be stored at least 50°C below their T_g to ensure physical stability (7,23). However, the current study shows that the situation might be different if drugs are mixed with an amorphous polymer (PVP). Recrystallization of the drug/PVP extrudates only occurred when the storage temperature was above the T_g (Table 6). Indomethacin/PVP extrudates remained amorphous for 2 months, even if the T_g (onset) was only slightly (approximately 10°C) above the storage temperature. The tolbutamide/PVP extrudate at 25°C/60% RH had a T_g of only 11.8°C, but was still amorphous after 2 months. This finding shows that prediction of physical stability based on the predicted T_g value alone may result in a wrong conclusion.

The stability prediction based on drug/PVP beaker melts, on the other hand, was correct for all four drug/PVP extrudates if residual crystallinity of the mixtures immediately after preparation of the beaker melts is recorded, and only an *increase* in residual crystallinity over storage time is taken as a predictor for recrystallization of the extrudate. This is a conservative prediction of the suitability of a drug candidate for melt extrusion because, in the case of the presence of residual crystallinity, seeding crystals increase the likelihood of further crystallization (24).

A possible explanation for the finding that tolbutamide extrudates remained amorphous is that the viscosity of the sample was still very high, although being in the rubbery state, and thus precluded recrystallization.

It should be pointed out, that in this study, only one polymer was used. Further studies should be performed using polymers with different physicochemical properties (e.g., different T_g).

Prediction of Chemical Stability

Chemical stability of the drug/PVP preparations was investigated for beaker melts and extrudates (Fig. 2). In general, decomposition values for the beaker melt samples were slightly higher than those for the extrudates. In the case of lacidipine, the more significant decrease

Table 7

Comparison of T_g *Values Derived from Predictive Methods to Extrudate Shown as* $T_{g_{predictive}}/T_{g_{extrudate}}(K/K)$

Drug	GT[a]	DSC	Beaker Melt	Extrudate T_g Predicted[b]	Predicted[b]/ Extrudate
Indomethacin	1.02	0.97	0.94	347	0.99
Lacidipine	1.01	1.01	0.97	352	1.00
Nifedipine	1.02	0.99	0.96	352	0.99
Tolbutamide	1.07	0.91	0.97	312	1.00
	1.03 ± 0.03	**0.97** ± 0.04	**0.96** ± 0.01		**1.0** ± 0.01

DSC, differential scanning calorimetry; GT, prediction of T_g based on expanded Gordon-Taylor equation (Eq. 2).

[a] Taking into account residual moisture.

[b] Combines DSC, beaker melt, and GT to predict the extrudate T_g.

in degradation of the extrudate was probably due to the increased total length of heating in the beaker melt (4 min), in an attempt to remove residual crystallinity, compared to extrusion residence time (2–3 min). In addition, the open nature of the beaker melt and poorer control of heating rate may explain the increased chemical degradation seen in all cases with this method compared to extrusion. Thus, beaker melts allow a conservative estimation of the chemical stability of the drug during extrusion.

Prediction of Dissolution

The dissolution rate of the beaker melt samples can be regarded as a conservative predictor for the dissolution rate of the extrudates. Apart from tolbutamide, the drug/PVP beaker melts showed an increase in dissolution of the drug compared to crystalline drug and drug/PVP physical mixture, but still underestimated the dissolution rates of the extrudates. The decreased dissolution from the drug/PVP beaker melts compared to the extrudates is probably due to the extrudates being 100% amorphous solid solutions. Whereas extrusion produced a transparent glassy solid with no crystallinity, beaker melts led to an opaque mass as the system lacked the required energy to plastify the polymer fully without causing decomposition.

CONCLUSION

A beaker melt test, followed by appropriate testing of the resultant material, can be used to predict the suitability of a drug for melt extrusion. In addition, the data derived from the beaker melt test may allow the melt extrusion process for the drug to be optimized more rapidly. However, incomplete homogeneity of the material in the test tends to underestimate the improvement in drug dissolution that can be expected from full-scale melt extrusion trials. DSC melting of drug provides T_g data for use in predictive equations (GT equation), but these values could be derived based on the relationship $T_g = 0.7\ T_m$. Accuracy of extrudate T_g prediction can be increased if combinations of DSC melt, beaker melt, and GT-derived glass transition values are used. Further investigations are required to explore the general application of the suggested screening methods as only one polymer and five drugs in one weight ratio of drug to polymer were investigated.

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