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# The effect of spray drying solutions of bendroflumethiazide/polyethylene glycol on the physicochemical properties of the resultant materials

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## Abstract

The physicochemical properties of co-spray dried bendroflumethiazide (BFMT)/polyethylene glycol (PEG) 4000 composites were investigated. The co-spray dried composites produced from all BFMT/polymer solutions were amorphous. BFMT/PEG 4000 10 and 20% systems consisted of smooth spherical particles approximately 0.5–4 mm in diameter. Spray drying resulted in no significant production of the main BFMT degradant, 5-trifluoromethyl-2,4-disulphamoylaniline (TFSA), and for composites consisting of 90% PEG 4000 by weight of total solids, spray drying appeared a superior method of production than the melt method which resulted in significant BFMT degradation. All BFMT/PEG compressed discs showed initial increased release of BFMT compared to discs of micronised BFMT alone, with the spray dried BFMT/PEG 4000 10% system showing initial rates two to three times that of BFMT alone. The physical stability of amorphous BFMT was reduced on inclusion of PEG 4000, recrystallisation occurring more quickly with increasing amount of PEG 4000 in the composites. PEG in the co-spray dried systems appeared to degrade on storage and recrystallised samples failed to show the presence of PEG by differential scanning calorimetry (DSC), X-ray powder diffraction (XRD) or GPC. DSC results were consistent with BFMT/PEG forming a eutectic combination rather than a monotectic system.

*Keywords:* Spray dried bendroflumethiazide/PEG composites; Stability; Amorphous; Crystallinity

## 1. Introduction

Coprecipitation of drugs of low solubility with water-soluble polymers has been extensively studied as a means of improving biopharmaceutically relevant physicochemical properties such as solubility, dissolution rate and membrane transport (Chiou and Riegelman, 1971; Serajuddin, 1999; Craig, 2002). Such coprecipitates, when prepared with the water-soluble amorphous polymer PVP and composed primarily of greater than 50% drug, often contain the drug in a high energy amorphous form (Simonelli et al., 1969; Corrigan and Timoney, 1975). Frequently, the spray drying process results in higher energy amorphous products (Corrigan et al., 1984, 1985; Corrigan, 1995) showing amorphous characteristics over a wider composition range, with improved functional properties such as particle size, compaction or dissolution rate. In contrast, corresponding coprecipitates or melts prepared using the crystalline water-soluble polymers polyethylene glycol (PEG) are generally predominantly crystalline in nature

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(Corrigan and Timoney, 1976) and do not show a plateau, indicative of the presence of an amorphous phase of drug, in the intrinsic dissolution rate versus composition diagram. PEG, because of its low melting point, is difficult to spray dry. Recently, we have successfully spray dried PEG 4000 from ethanol solution and also shown that co-spray dried lactose/PEG systems of low PEG content were primarily amorphous (Corrigan et al., 2002). There are very few examples of PEG/amorphous drug solid dispersion systems (Law et al., 2001). To our knowledge, there are no examples, previous to this publication, of amorphous PEG/amorphous drug solid dispersion systems. Therefore, it was of interest to spray dry drug/PEG systems in an attempt to prepare totally amorphous systems. Such amorphous systems are likely to have higher energy and therefore show increased solubility (Hancock and Parks, 2000) and increased dissolution rates (Corrigan et al., 1985) when compared to their crystalline counterparts and therefore should show higher bioavailability (Fukuoka et al., 1987). It has previously been shown that spray drying the thiazide diuretics hydroflumethiazide and bendroflumethiazide (BFMT) from ethanol resulted in amorphous products with increased solubility (Corrigan et al., 1984). Several other thiazide diuretics were spray dried such as chlorthiazide, hydrochlorthiazide and cyclopenthiazide. The lower molecular weight thiazides (i.e. chlorthiazide, hydrochlorthiazide and hydroflumethiazide) formed amorphous phases less readily and had poor physical stability. Chlorthiazide only formed an amorphous phase when spray dried with PVP while hydrochlorthiazide spray dried alone was amorphous stable for only 24 h. The larger molecular weight thiazides such as BFMT and cyclopenthiazide readily gave amorphous phases on spray drying and were physically stable even after 12 months (Corrigan et al., 1984).

The objective of this work was to prepare spray dried BFMT/PEG systems to ascertain if amorphous BFMT/PEG composites could be formed with improved dissolution characteristics relative to BFMT alone. BFMT was chosen as it has a lower solubility than hydroflumethiazide and has been shown to be amorphous when spray dried alone. Furthermore, previous reports suggested that coprecipitates of BFMT with PEG may be chemically unstable and therefore spray drying may result in a more stable product (Frontini and Mielck, 1992, 1997a).

## 2. Experimental

### 2.1. Materials

BFMT was kindly provided by Leo Laboratories, Ireland, PEG 4000 was purchased from Riedel de Haën (Germany). Physical mixes were prepared using sub 63 mm mesh sieved powders mixed in a Turbula Mixer$^{TM}$ for 5 min.

All spray dried systems were analysed by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRD) within 1 h of production. They were then stored at controlled temperature and humidity conditions using incubators and saturated salt solutions (Nyqvist, 1983). Sodium chloride was used to create high humidity conditions (75% RH). The effect of storage was investigated at 30 °C 75% RH and 45 °C 75% RH.

5-Trifluoromethyl-2,4-disulphamoylaniline (TFSA) (the main degradation product of BFMT) was prepared according to the method of Hassan (1983).

### 2.2. Spray drying methodology

BFMT was spray dried as a 2.5% w/v solution from 95% ethanol, using a Büchi 191 with inlet air temperature 78–79 °C, outlet temperature 58–62 °C, pump setting 20%, airflow rate of 600 Nl/h and aspirator rate 100%. Systems containing 10, 20 or 30% PEG by weight of BFMT were spray dried as 2.5% w/v solutions from 95% ethanol under similar conditions except that the inlet temperature was 78–80 °C and the outlet temperature was 56–62 °C. A system containing 90% PEG by weight of BFMT was spay dried as a 2.5% w/v solution from 95% ethanol, with inlet air temperature 71–72 °C, outlet temperature 42–45 °C, pump setting 45%, airflow rate of 600 Nl/h and aspirator at 100%.

### 2.3. Assessment of physicochemical properties

X-ray powder diffraction measurements were made on samples in low background silicon mounts, which consisted of cavities 0.5 mm deep and 9 mm in diameter (Bruker AXS, UK). The Siemens D500 Diffractometer consists of a DACO MP wide-range goniometer with a 1.0° dispersion slit, a 1.0° anti-scatter slit and a 0.15° receiving slit. The Cu anode X-ray tube was operated at 40 kV and 30 mA in combination with a Ni filter to give monochromatic Cu Kα X-rays. Measurements were generally taken from 5° to 35° on the $2\theta$ scale at a step size of 0.05°/s for qualitative analysis.

Differential scanning calorimetry (Mettler Toledo DSC 821$^{e}$) using closed 40 μl aluminium pans with three vent holes and thermogravimetric analysis (TG) (Mettler TG 50 linked to a Mettler MT5 balance) using open pans, were performed on accurately weighed samples (5–10 mg). Samples were run at a heating rate of 10 °C/min under nitrogen purge.

Modulated temperature DSC (Q1000 Tzero$^{TM}$ TA Instruments DSC) was performed using closed aluminium pans with three vent holes on accurately weighed samples (5–10 mg) under nitrogen purge. A heating rate of 5 °C/min, a modulation amplitude of 0.5 °C and a period of 50 s were used.

Dissolution studies were performed using the paddle dissolution apparatus (USP, 2000) (Sotax AT7 dissolution bath) at 37 °C with a paddle rotation speed of 50 rpm. Discs were prepared from 200 mg of powder using a 13 mm punch and die set and compressing in a Perkin-Elmer hydraulic press at a pressure of 7 tonnes for 1–2 min. The discs were mounted in stainless steel cylindrical holders with one end filled with paraffin wax so that only one surface was exposed to the dissolution medium. The dissolution medium consisted of 400 ml of buffer pH 2 (Frontini and Mielck, 1992, 1997a).

The samples from the dissolution tests were analysed for BFMT content by UV analysis, having established, by HPLC, that no significant increase in TFSA (the main degradation product) occurred over the time course of the dissolution run.

HPLC analysis of BFMT and TFSA were performed according to the method of Frontini and Mielck (1992).

UV analysis of BFMT at 274 nm was performed using a Hewlett-Packard 8452A photodiode array UV-Vis spectrophotometer.

Scanning electron microscopy (SEM) was performed using a Hitachi S-3500N variable pressure scanning electron microscope.

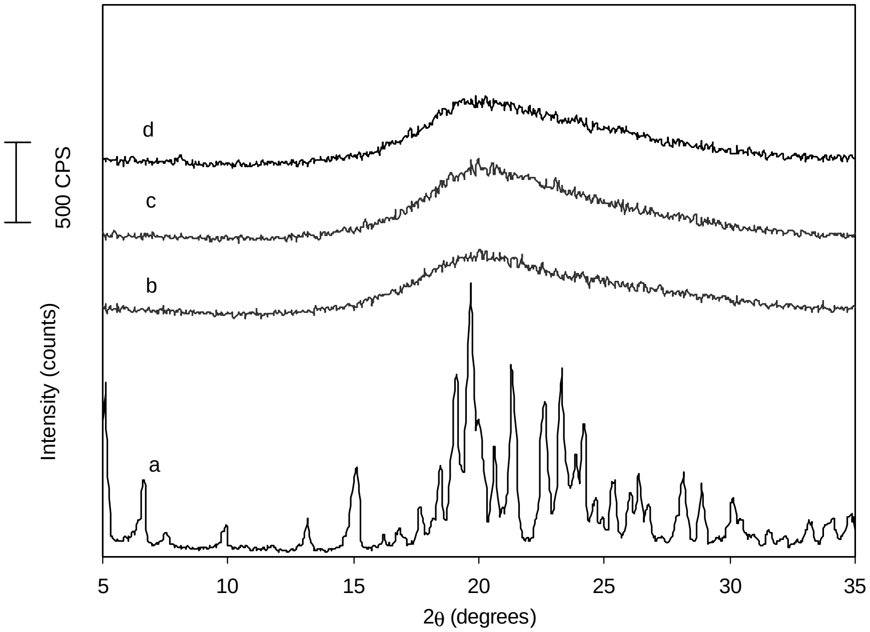

Fig. 1. XRD scans of (a) physical mix BFMT/PEG 4000 10%; (b) spray dried BFMT/PEG 4000 10%; (c) spray dried BFMT/PEG 4000 20%; (d) spray dried BFMT/PEG 4000 30%.

## 3. Results and discussion

### 3.1. Co-spray dried BFMT/PEG 4000 systems

Systems containing 0, 10, 20, 30 and 90% PEG by weight of total solids were spray dried. The lack of peaks by XRD confirmed that BFMT spray dried alone was amorphous, as previously reported (Corrigan et al., 1984). DSC data showed a relaxation endotherm indicative of the glass transition temperature, with an onset temperature at approximately 120 °C, followed by an exotherm (recrystallisation from amorphous state) and then the melting endotherm, which had an onset temperature at approximately 220 °C. Fig. 1 shows the XRD scan of co-spray dried BFMT/PEG 4000 composites (containing 10, 20 and 30% PEG). The systems were all amorphous, indicated by the lack of peaks indicative of crystallinity. No peaks indicative of crystalline PEG were visible which contrasts with the XRD data, previously reported (Corrigan et al., 2002), for lactose/PEG systems containing 20 and 30% PEG in which peaks indicative of crystalline PEG were evident.

DSC scans of the co-spray dried samples are shown in Fig. 2. The 10% PEG system showed two small endothermic events with onset temperatures at approximately 205 and 210 °C. A broad endotherm at approximately 90 °C was observed. This endotherm is at too high a temperature to be due to the melting of PEG. A DSC scan of a physical mix of BFMT/PEG 10% is shown in Fig. 2 (scan d), the endotherm in the PEG melting region indicating that DSC can readily detect such a concentration of PEG in a mixed system. The spray dried BFMT/PEG 20% system (Fig. 2, scan b) showed a small melting endotherm at approximately 170 °C followed by a broader double endotherm at approximately 200 °C. A broad endotherm is present at approximately 70 °C which is also at too high a temperature to be due to the presence of PEG. No exotherms or endotherms in the PEG

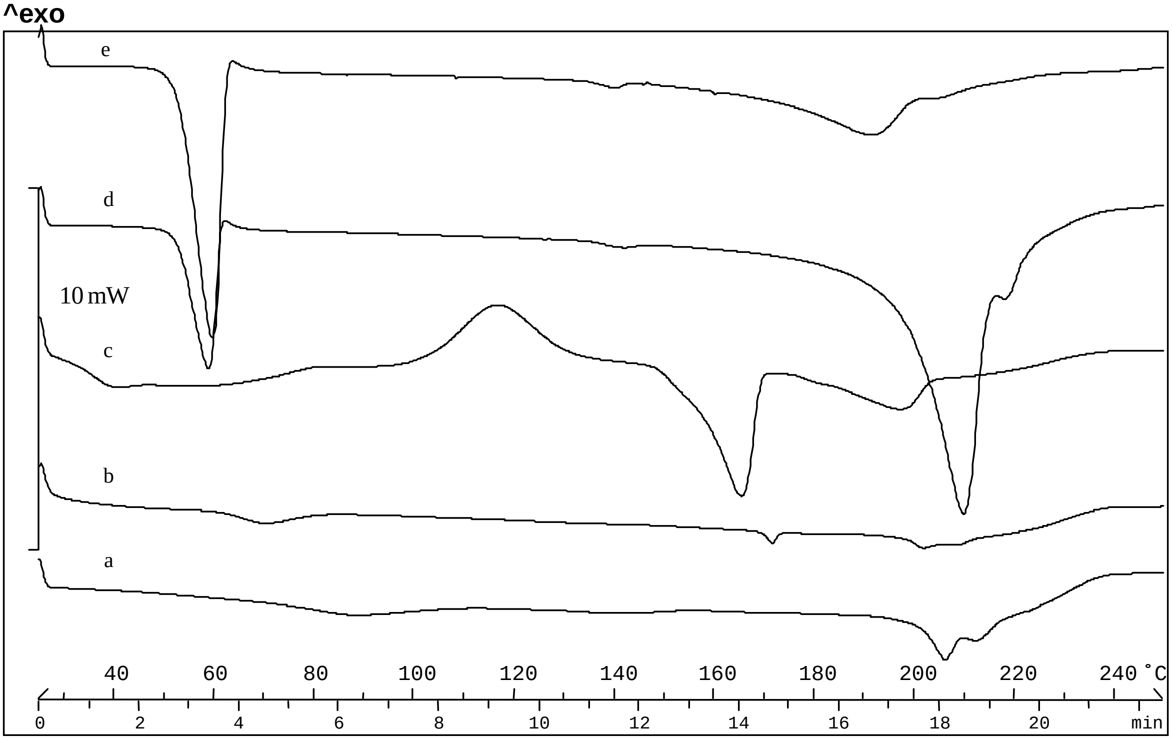

Fig. 2. DSC scans of (a) spray dried BFMT/PEG 4000 10%; (b) spray dried BFMT/PEG 4000 20%; (c) spray dried BFMT/PEG 4000 30%; (d) physical mix BFMT/PEG 4000 10%; (e) physical mix BFMT/PEG 4000 30%.

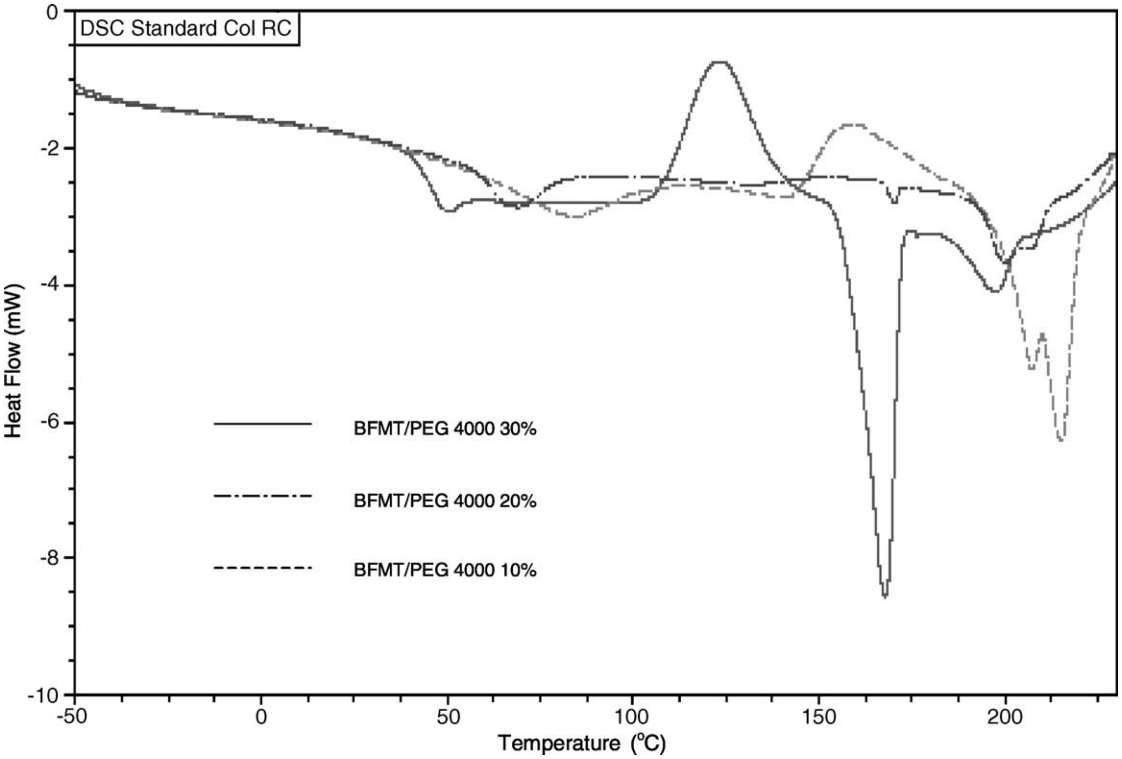

Fig. 3. Modulated temperature DSC scan of spray dried BFMT/PEG 4000 10, 20 and 30%.

melting region were observed in either the 10 or 20% spray dried PEG system. The 30% PEG-containing system (Fig. 2, scan c) showed an exotherm at approximately 120 °C prior to the melting of BFMT which occurred at approximately 150 °C followed by a second endotherm which peaked at approximately 200 °C. A change in the baseline was visible in the PEG melting region but did not resemble melting of PEG as seen in the equivalent physical mix, the physical mix of BFMT/PEG 30% also being shown in Fig. 2 (scan e). The onset melting temperature of pure unprocessed BFMT by DSC was 229 °C. Physical mixes of BFMT with PEG 4000 (Fig. 2) resulted in the BFMT melting endotherms occurring at lower onset temperatures than BFMT alone indicating that the presence of PEG reduced the temperature of BFMT melting. The physical mixes showed a second melting endotherm following or overlapping with the BFMT melting endotherm as was the case with the spray dried systems. This second endotherm is likely due to degradation of BFMT on heating. No obvious glass transitions were visible in the spray dried BFMT/PEG systems, although changes in the baseline were observed in the 40–90 °C temperature region. A change in the baseline was especially obvious in the 30% PEG system and this could have been due to the glass transition.

Modulated temperature differential scanning calorimetry, which is known to be superior to conventional DSC for measuring glass transitions (Craig, 1995), was performed on spray dried BFMT/PEG 10, 20 and 30% systems. Fig. 3 shows the total heat flows recorded using the modulated temperature DSC for these systems. Samples that have been cooled at a rate very different from their subsequent heating rate often show enthalpic relaxation peaks in the glass transition region (Verdonck et al., 1999). Verdonck et al. (1999) report that this relaxation peak can be large enough to conceal the variation of the heat capacity at the glass transition, and the glass transition may be misinterpreted as a melting transition. Fig. 4 shows the separation of reversing and non-reversing

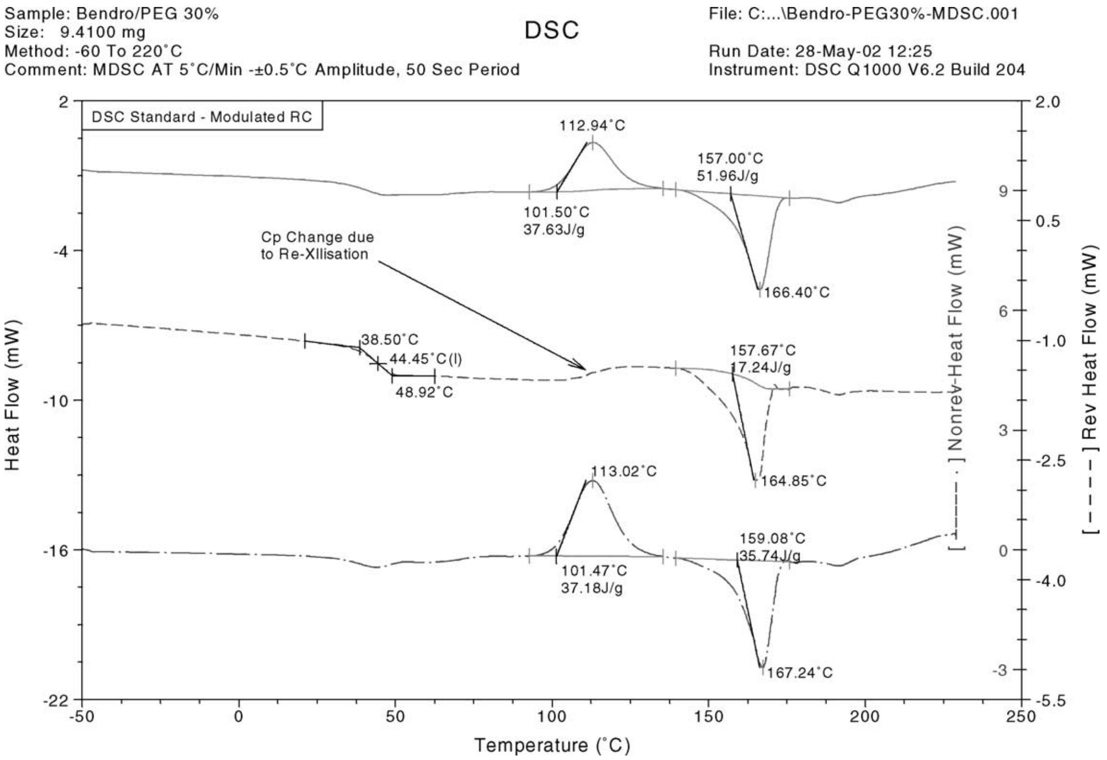

Fig. 4. Modulated DSC scan of spray dried BFMT/PEG 30% showing separation of reversing (middle scan) and non-reversing (lower scan) heat flows.

heat flow signals for the modulated DSC scan of the 30% PEG sample, showing separation of the change in heat capacity at the glass transition (shown in the reversing heat flow in Fig. 4) from the enthalpic relaxation (shown in the non-reversing heat flow in Fig. 4).

From the modulated DSC experiments, it appeared that the endotherms observed by conventional DSC in the 40–90 °C temperature region were due to enthalpic relaxations which masked the glass transitions. The glass transition temperatures appeared to decrease as the amount of PEG in the composites was increased. The BFMT/PEG 4000 10% system showed a glass transition at approximately 83 °C, the BFMT/PEG 4000 20% showed a glass transition at approximately 69 °C and the BFMT/PEG 4000 30% systems showed a glass transition at approximately 45 °C.

SEM micrographs of spray dried BFMT/PEG 4000 systems are shown in Fig. 5. BFMT/PEG 4000 10 and 20% systems consisted of smooth spherical particles approximately 0.5–4 μm in diameter. The spheres present in the 10% PEG system although smooth surfaced did show some surface dimpling. The BFMT/PEG 4000 30% composite did not consist of distinct spheres but appeared to consist of flakes of fused material.

Prior to dissolution testing discs were analysed by XRD. All spray dried systems remained amorphous following compression into discs and discs of physical mixes showed similar XRD patterns to powders of physical mixes.

Intrinsic dissolution studies were performed on crystalline and spray dried BFMT, and equivalent physically mixed BFMT/PEG and co-spray dried systems. The BFMT/PEG 30% discs swelled and could not be retained in the holders. The dissolution profiles for the other systems are shown in Fig. 6.

Spray drying resulted in a high energy form of BFMT, with spray dried BFMT showing initial

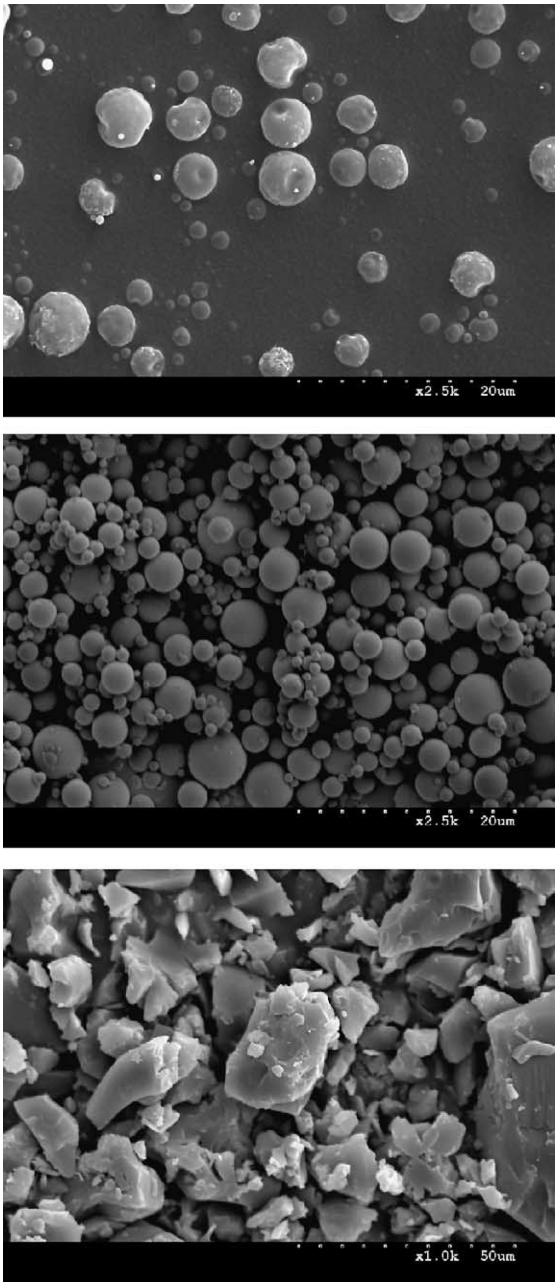

Fig. 5. SEM micrographs of spray dried BFMT/PEG 4000 systems. BFMT/PEG 4000 10% (top); BFMT/PEG 4000 20% (middle); BFMT/PEG 4000 30% (bottom). Note the lower magnification of the BFMT/PEG 4000 30% micrograph.

increased release of BFMT compared to micronised crystalline BFMT. All BFMT/PEG compressed discs showed initial increased release of BFMT compared to discs of micronised BFMT alone, with the spray dried BFMT/PEG 4000 10% system showing initial rates two to three times that of BFMT alone.

The spray dried BFMT/PEG 10% system gave a significantly higher release rate, over the first 15 min, than the 20% PEG spray dried system or the physical mix BFMT/PEG systems, which in turn gave significantly higher release rates than micronised BFMT. Profiles of the spray dried systems were nonlinear, the dissolution rate declining over time, reflecting recrystallisation of the components and the more rapid dissolution of the polymer. This was confirmed by XRD of the discs following dissolution testing, which showed the presence of crystalline BFMT but no evidence of the presence of PEG 4000. Discs of the physical mixes after dissolution testing were analysed by XRD and while crystalline BFMT was visible, peaks due to PEG 4000 were not observed.

### 3.2. Phase diagram

Phase diagrams are used to characterise the phases present in binary systems. Phase diagrams produced from melting data obtained from thermal analysis of physical mixtures have been shown to correlate well with those produced from fused or evaporated mixtures (Guillory et al., 1969). Physical mixes of BFMT/PEG 4000 were prepared and heated by DSC. Melting point data was obtained from the heating cycle, since BFMT degrades when heated past its melting point. Onset melting temperatures were determined at different compositions, i.e. mole fraction PEG (based on unit molecular weight PEG) and these are shown in Fig. 7. The BFMT/PEG phase diagrams appeared to resemble monotectic systems. Monotectic systems have been described by several authors (Kaur et al., 1980; Chatham, 1985; Craig, 1989; Venkataram and Rogers, 1984; Najib and Suleiman, 1989). Monotectic systems have been described as eutectic systems where one “arm” of the diagram is missing and the lower melting component replaces the eutectic composition. Alternatively, eutectic systems are two phase systems where the two components are miscible in all proportions in the liquid state but are totally

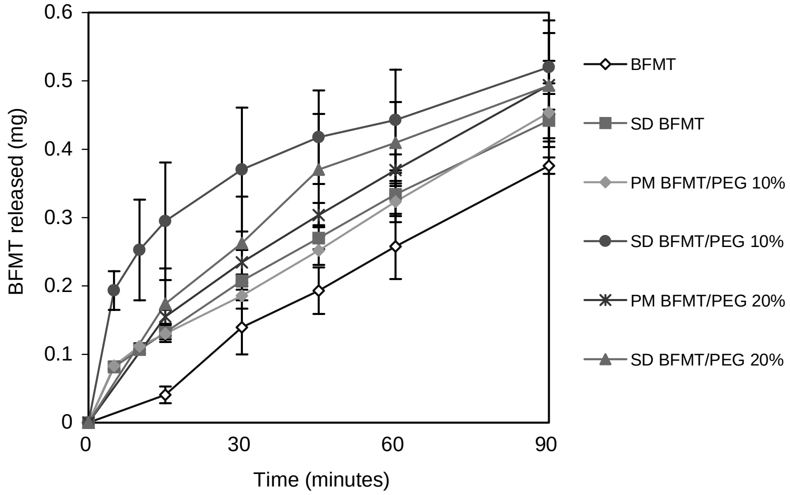

Fig. 6. Dissolution of spray dried (SD) and physical mixes (PM) of BFMT/PEG 4000, SD BFMT and BFMT alone at 37 °C in pH 2 media.

immiscible in the solid state (Reisman, 1970). The eutectic point is the composition that gives the lowest melting and is below that of either of the two pure components and when that composition melts it gives a single melting event. The Le Chatelier–Schroder–van Laar equations (Smith, 1977) describe the melting curves of eutectic binary systems (Eqs. (1) and (2)).

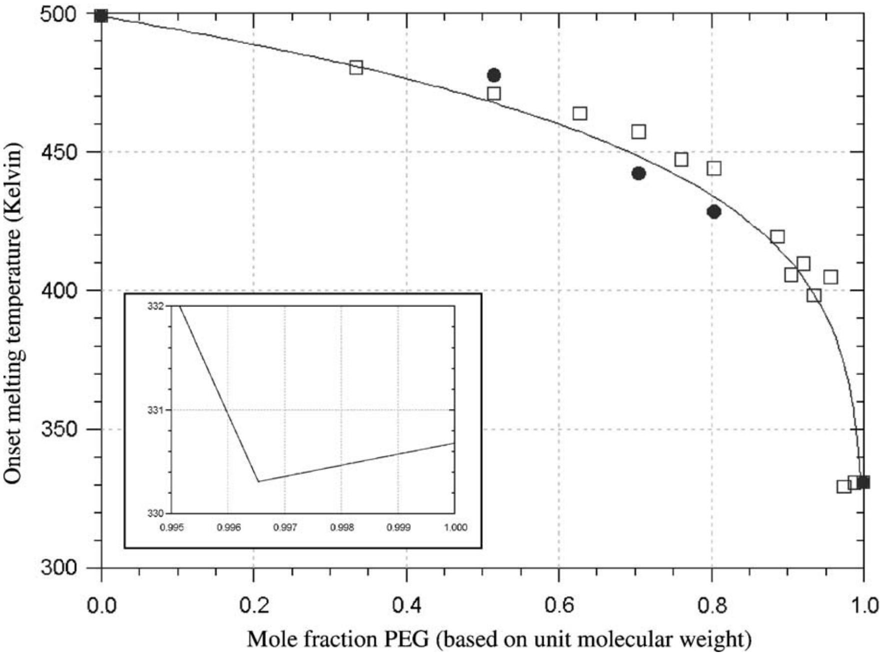

Fig. 7. Simulation of BFMT/PEG 4000 eutectic system and actual data for physical mixes and spray dried BFMT/PEG 4000 systems obtained using onset melting temperatures with inset showing simulation on expanded scale for mole fraction between 0.995 and 1. (☐) Data from physical mixes; (●) data from spray dried systems; (—) simulation.

Melting curve $T_a$:

$$T = \frac{\mathrm{MP_a}}{1 - (R \cdot \mathrm{MP_a}/H_a)\ln X} \quad (1)$$

where $X$ is the mole fraction of component a, $\mathrm{MP_a}$ is the melting temperature of component a and $H_a$ is the enthalpy change of component a.

Melting curve $T_b$:

$$T = \frac{\mathrm{MP_b}}{1 - (R \cdot \mathrm{MP_b}/H_b)\ln(1 - X)} \quad (2)$$

where $\mathrm{MP_b}$ is the melting temperature of component b and $H_b$ is the enthalpy change of component b.

For BFMT and PEG, the values of the melting point and the heat of fusion were determined experimentally and used to generate the phase diagram using Eqs. (1) and (2). $R$, the gas constant was 8.315. The experimentally derived onset melting temperature and heats of fusion used to generate the phase diagram were 330.68 K and 8448 J/mol, respectively, for PEG 4000 and 498.88 K and 44925 J/mol, respectively, for BFMT.

The onset melting temperature data was plotted versus composition and the predicted profile is shown Fig. 7, together with the actual data points for physical mixes and spray dried systems. The coefficient of determination value of 0.927, for the fit of the experimental onset melting temperatures of the physical mixes to the simulated curve predicted from Eqs. (1) and (2), was quite good, and improved to 0.991 for the spray dried systems. Close examination of the simulated curve in Fig. 7 shows that the system does in fact conform to a eutectic profile with the eutectic point at a PEG mole fraction of 0.9965.

### 3.3. Physical stability of BFMT/PEG 4000 systems

Samples of spray dried BFMT and co-spray dried BFMT/PEG 4000 10, 20 and 30% were stored at 30 °C and at a relative humidity of 75% (Nyqvist, 1983). DSC analysis was used to monitor recrystallisation of the samples after storage at 30 °C 75% RH for various time periods. Spray dried BFMT remained amorphous for over 6 months, while the 10% PEG 4000 system showed a recrystallisation exotherm after 29 days but no exotherm by day 31 of storage. The 20% PEG 4000 system retained the recrystallisation exotherm at 10 days of storage but no recrystallisation exotherm thereafter. On analysis of the 30% PEG system following 18 h of storage no recrystallisation exotherm was evident. The presence of PEG in the composites appeared to destabilise the amorphous BFMT with higher weight ratios of PEG causing faster recrystallisation. This result is in contrast with the observed behaviour of lactose/PEG co-spray dried systems (Corrigan et al., 2002), where the presence of PEG at low concentrations, when it was mainly amorphous (lactose/PEG containing 5 or 10% PEG 4000 by weight of solids), appeared to retard crystallisation, while crystallisation of lactose was only accelerated at higher concentrations of PEG (lactose/PEG 20%).

Fig. 8 shows a plot of the DSC enthalpy changes of the exotherms versus time for spray dried BFMT and spray dried BFMT/PEG 4000 systems when stored at 30 °C 75% RH. The recrystallisation exotherm was not initially evident in the 10 and 20% PEG systems following spray drying which may indicate that initially these systems are stable on heating. Furthermore, the absence of an exotherm initially in the 10 and 20% PEG systems is consistent with glass solutions. On storage, exotherms, which were not present initially (Fig. 2), became evident and the enthalpy change associated with these exotherms increased initially prior to decreasing eventually to zero at later storage times when the samples had fully recrystallised. The 20% PEG system was the slowest to reach its maximum enthalpy change associated with the recrystallisation exotherm. Recrystallisation in the 10% PEG system stored at 30 °C 75% RH did not appear to be a co-operative process but appeared gradual with exothermic peaks becoming smaller over time (Fig. 8). Buckton and Darcy (1995) described the recrystallisation of amorphous lactose as occurring simultaneously throughout the powder bed in a co-operative process. They studied the recrystallisation of amorphous lactose when the amorphous material was divided by different additives and found that the lactose recrystallised all at one time even when it was physically divided into two separate regions by the additives.

From the modulated DSC experiments (Fig. 3), it appeared that the glass transition temperatures of the systems decreased with increasing PEG content (i.e. PEG acts as a plasticiser). Absorbed water generally acts as a plasticiser, lowering the glass transition of amorphous materials until eventually, when enough

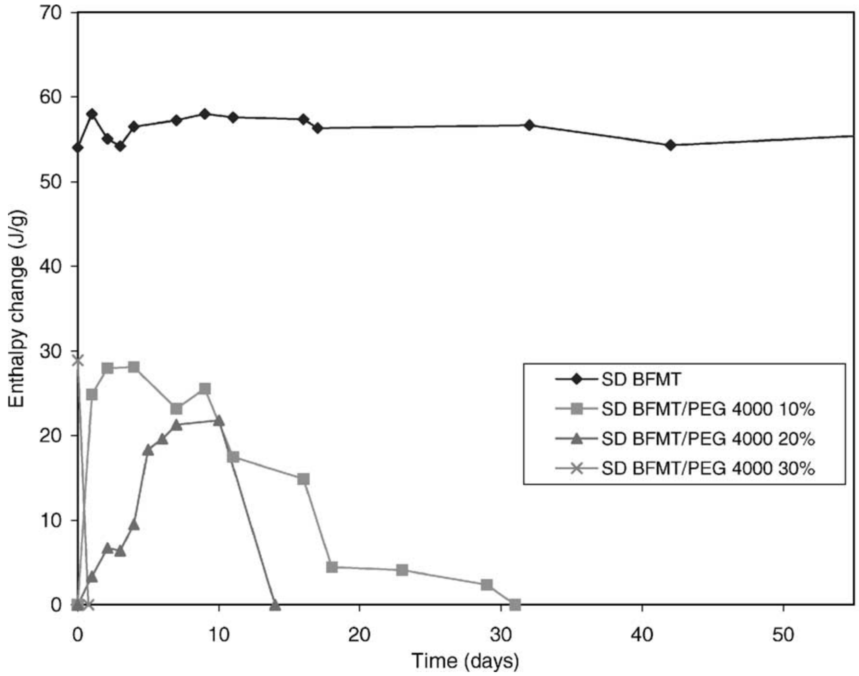

Fig. 8. DSC recrystallisation data (based on exothermic enthalpy change) for spray dried BFMT and BFMT/PEG 4000 systems at 30 °C 75% RH.

water is absorbed, the glass transition becomes lowered to the storage temperature and the material recrystallises. Since the 30% PEG system has the lowest glass transition temperature, the time for the absorption of water to lower this already lowered glass transition will be faster than for the other systems with higher initial glass transition temperatures. Therefore, since the glass transition temperatures of the spray dried systems decreased with increasing PEG, the system with the highest amount of PEG (the lowest glass transition) will recrystallise first and that with the lowest amount of PEG (i.e. the highest initial glass transition) will take the longest time to recrystallise. This was shown to be the case in the storage study at 30 °C 75% RH (Fig. 8).

From XRD scans of spray dried BFMT/PEG 20%, it was observed that the sample stored at 30 °C 75% RH remained amorphous following 7 days of storage. XRD following 5 weeks of storage showed peaks indicative of crystallinity (Fig. 9, scan e). No peaks indicative of PEG were visible in the stored samples by XRD. A physical mix of BFMT/PEG 20% is shown in Fig. 9 (scan b), the peak at approximately 23.4° $\theta$ being due to the presence of PEG. DSC of the 30 °C 75% RH sample following 5 weeks of storage also failed to show peaks indicative of the presence of PEG.

No peaks by XRD (Fig. 9, scan d) nor by DSC were visible for PEG in the BFMT/PEG 10% samples stored at the 45 °C 75% RH for 4 days. GPC analysis of amorphous spray dried BFMT/PEG systems confirmed the presence of PEG 4000 in the composites. Following storage, when recrystallised samples failed to show the presence of PEG by DSC and XRD, GPC of these samples also did not detect the presence of PEG. It is likely that the PEG has degraded. A similar phenomenon was observed when lactose/PEG samples were stored at high temperatures and high relative humidities.

The stored spray dried samples shown in Fig. 9 had not fully recrystallised as indicated by the lack of many peaks corresponding to crystalline BFMT and the background halo underlying the peaks which were present. An XRD scan of TFSA, the main degradation product of BFMT, is shown in Fig. 9 (scan c), showing peaks not visible in the recrystallising BFMT/PEG samples (at approximately 11° and 27° 2$\theta$). Therefore,

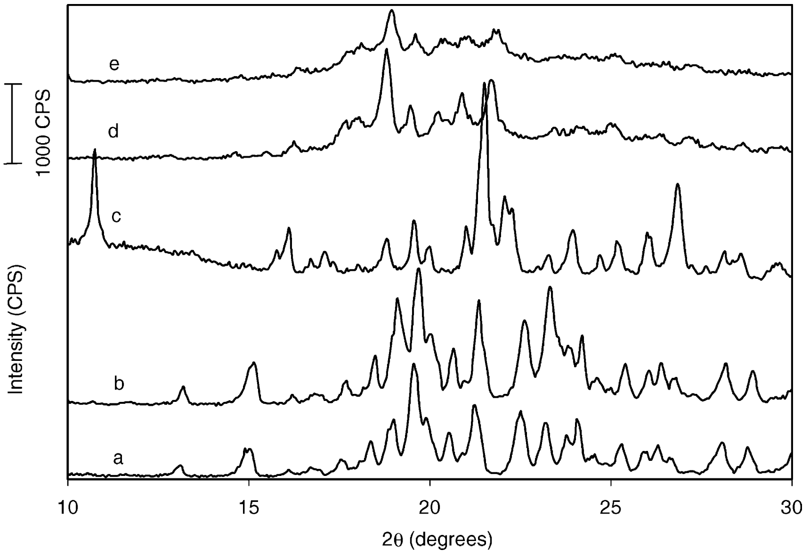

Fig. 9. XRD of (a) BFMT; (b) physical mix of BFMT/PEG 4000 20%; (c) TFSA; (d) spray dried BFMT/PEG 4000 20% stored at 45 °C 75% RH for 4 days; (e) spray dried.

amorphous BFMT does not appear to recrystallise to its degradation product TFSA.

### 3.4. Chemical stability of BFMT/PEG 4000 systems

Frontini and Mielck (1997a) prepared solid dispersions of BFMT/PEG 6000 using both a melt method and a solvent evaporation method. They used drug:carrier weight ratios of 10:90 BFMT:PEG 6000 and described their system as X-ray amorphous. Frontini and Mielck (1997b) also described the chemical instability of BFMT in the presence of PEG with hydrolysis of the BFMT to TFSA and hydroflumethiazide (HFMT). In our laboratory, we prepared a similar weight ratio of BFMT:carrier using the melt method described by Frontini and Mielck (1997a) but replacing PEG 6000 with PEG 4000. The product obtained was cream to yellow in appearance. XRD analysis showed the BFMT to be amorphous but the PEG 4000 to be crystalline. For comparison purposes a 10:90 weight ratio BFMT:PEG 4000 was spray dried. Fig. 10 shows the XRD scans of the systems prepared by both methods (i.e. the spray drying method and the melt method). The spray drying method gave similar results to the melt method by XRD, i.e. peaks indicative of crystalline PEG but no peaks indicative of crystalline BFMT. However, the spray drying method did result in significantly lower intensity peaks indicative of a reduction of PEG crystallinity by this method of production.

The spray dried BFMT/PEG 90% system appeared white in colour, similar to the other spray dried systems containing different weight ratios, in contrast to the creamy/yellow system obtained by the melt method. HPLC analysis was performed on both systems using the method of Frontini and Mielck (1992) and a significant amount of TFSA (main degradation product) was found in the sample prepared by the melt method. HPLC of the melt-produced system consisted of 0.5% w/w TFSA. This was approximately 64 times the amount present in the equivalent spray dried system. The other spray dried BFMT/PEG 4000 systems were also analysed by HPLC to determine whether the spray drying method resulted in degradation of the drug. All systems showed no significant increase in TFSA compared to the starting material.

The melt method involved heating to 80 °C whilst spray drying involved an inlet temperature of 79–80 °C. An inlet temperature of 79–80 °C, however, resulted in an outlet temperature of only 60–66 °C. It is generally recognised that spray drying is a suitable method for processing many heat sensitive materials (Broadhead et al., 1992). Generally, the particles reach a maximum temperature which is well below the

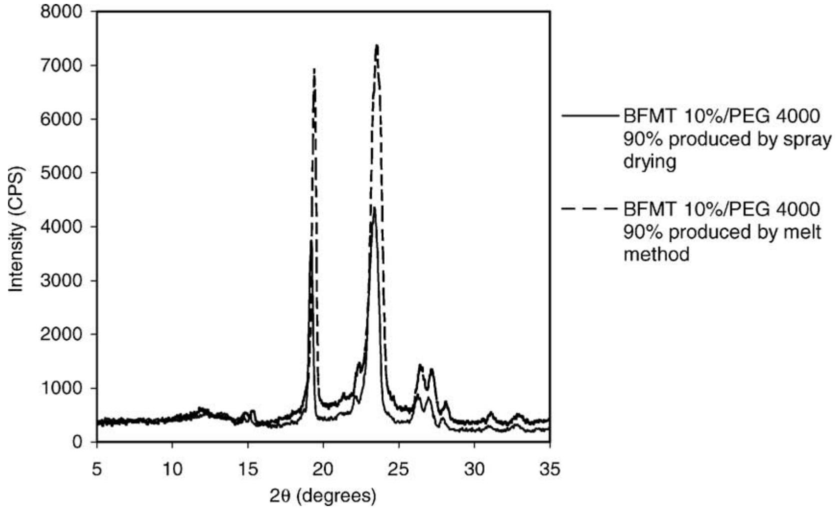

Fig. 10. XRD scans of BFMT/PEG 4000 90% prepared by both the spray dried and melt method.

outlet temperature of the spray drier (Masters, 1985). The superiority of the spray drying method over the melt method for production of BFMT/PEG composites with respect to TFSA production is probably due to the short drying times and minimum exposure to heat.

## 4. Conclusions

Spray drying of BFMT with the normally crystalline polymer PEG, at concentrations of 10, 20 and 30% PEG, can result in amorphous composites, which may be glass solutions at low PEG loadings. Spray drying results in no significant production of the main BFMT degradant, TFSA, and for composites consisting of 90% PEG 4000 by weight of total solids spray drying appears a superior method of production than the melt method which results in significant BFMT degradation.

The physical stability of amorphous BFMT is reduced on inclusion of PEG 4000, recrystallisation occurring more quickly with increasing amount of PEG 4000 in the composites. PEG degraded on storage and was not detected in recrystallised samples. All BFMT/PEG compressed discs showed initial increased release of BFMT compared to discs of compacted BFMT alone with the spray dried BFMT/PEG 4000 10% system showing initial rates two to three times that of BFMT alone.

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