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The impact of low levels of amorphous material (< 5%) on the blending characteristics of a direct compression formulation

Lesley Mackin [a,*], Soisurin Sartnurak [a], Iwan Thomas [b], Stephen Moore [c]

[a] *Pharmaceutical and Analytical Sciences, Pharmacia R&D, Chicago, IL 60077, USA*
[b] *Process Development, Pharmacia, Morpeth, UK*
[c] *QA Department, Pharmacia, Morpeth, UK*

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Abstract

During the manufacture of tablets for registration stability studies, it was observed that blends manufactured using milled active frequently failed the blend content uniformity criteria (actual relative standard deviation (RSD) of 4–15%) at the prelubrication stage, whereas unmilled active batches were consistently giving very good blend uniformity results (RSD < 3.5%). The addition of magnesium stearate dramatically improved the blending characteristics of the milled batches, suggesting that milling had altered the surface properties. A hypothesis was presented that amorphous material was created during the milling of the active batches, which subsequently recrystallised over a short period of time e.g. days/hours. Following recrystallisation the batches did not exhibit the same physical properties as the unmilled actives, and this resulted in the drug product batches failing to meet their pre-lubrication acceptance criteria for blend content uniformity. This paper describes the results of a laboratory scale study to investigate this hypothesis and therefore explain the processing issues that were observed during the manufacture of the registration stability batches with milled active batches.

Keywords: Milling; Amorphous; Blend content uniformity; Surface properties; Dynamic vapour sorption; Isothermal microcalorimetry

1. Introduction

It is well documented in the literature that milling can cause disruption or activation of the crystal structure, leading to various degrees of disorder (Waltersson and Lundgren, 1985; Sebhatu et al., 1994; Saleki-Gerhardt et al., 1994). If this disorder is more extensive than the occasional molecular dislocation, it can be viewed as an amorphous region within the crystal structure. Amorphous and crystalline forms of the same chemical entity may behave differently when processed, especially when the amorphous regions are

* Corresponding author. Present address: Astrazeneca, Silk Road Business Park, Charter Way, Macclesfield, Cheshire SK10 2NA, UK. Tel.: +44-1625-230595.
E-mail address: lesley.mackin@astrazeneca.com (L. Mackin).

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concentrated at the surfaces of solid particles. Milling, therefore, has the potential to influence a number of physical powder properties, including flow, cohesiveness, and electrostatic charge (Briggner et al., 1994; Feeley et al., 1998; Craig et al., 1999). To date there is very little published work relating the physical properties changes resulting from surface disorder to differences in the behaviour of an active in a drug product formulation.

Xemilofiban is an oral antithrombotic agent, which was a clinical development candidate for Pharmacia. Xemilofiban active batches were manufactured into tablets of 10 and 20 mg strengths using a direct compression approach. In order to meet the particle size specification, the active batches were milled to break down large agglomerates that formed during the drying process. After transfer of the active technology to the commercial site, the drying equipment was upgraded and the milling step was removed from the manufacturing process. Drug product batches were therefore manufactured using both milled and unmilled active batches, although all batches met the same particle size specification and there was no significant difference between their particle size distributions (PSD).

During the manufacture of xemilofiban tablets for registration stability studies the majority of the drug product batches manufactured with milled active failed to meet the blend content uniformity acceptance criteria with relative standard deviation (RSD) values ranging from 4 to 15% at the 40 min (pre lubrication) blend stage. In addition, in one batch, loose aggregates with a high chemical content (300–500% of theoretical concentration) were found on the blend surface. Following an additional 10 min of blending with magnesium stearate, all but one of the blends met the blend content uniformity acceptance criteria. In contrast product batches manufactured with unmilled active met the blend content uniformity acceptance criteria at both the pre and post lubrication stages with blend RSD's less than 3.5%.

A comprehensive characterisation study was performed on xemilofiban active batches that were used in the drug product registration stability batches. The characterisation study found that the physical properties of the batches studied were comparable, e.g. crystal form, PSD, surface area, although minor differences using techniques such as moisture sorption analysis, scanning electron microscopy (SEM) and isothermal microcalorimetry, were found. These differences correlated with the milling required to meet the particle size specification, as well as their processing behaviour.

The characterisation study described above was performed approximately 6 months after the active batches had been milled and at this time no amorphous material was found. However, a hypothesis was presented that amorphous material may have been created during the milling of xemilofiban active batches, which subsequently recrystallised over a short period of time e.g. days/hours. The recrystallised batches exhibited different physical properties compared with the unmilled actives, resulting in the drug product batches failing to meet their pre lubrication acceptance criteria.

In order to investigate this hypothesis, a laboratory scale study was performed in which a batch of active was milled using different milling equipment. Following milling the amount of amorphous material was determined, and then allowed to recrystallise prior to being used in xemilofiban 10 mg powder blends to mimic what was thought to have occurred during the manufacture of the registration stability batches. In addition the recrystallised batches were fully characterised (e.g. crystal form, PSD, surface area, interaction with moisture) to investigate similarities with the active batches used in the manufacture of xemilofiban tablets.

The aim of this study was to investigate the hypothesis that amorphous material was created during milling which subsequently recrystallised to give crystals with different surface and hence processing properties and therefore explain the blend content uniformity failures observed during the manufacture of the registration stability batches

2. Materials and methods

2.1. Preparation of milled batches

Xemilofiban active batch S109080 was selected as the control for this study as it had been used in the registration stability campaign without any blending issues. This batch of active was processed using a filter drier and as such did not require milling to meet the particle size specification. The batch had a mean particle size of 7 μm with 90% of the particles less than 15 μm as determined by a light scattering technique.

The lab scale milling equipment and conditions were selected on the basis that they would produce amorphous regions on the particle surface without significantly affecting the particle size and surface area. Any changes in the processing attributes of the batches could therefore be correlated with the amorphous material generated through milling and its subsequent recrystallisation and not to changes in other physical properties (e.g. size, shape, area).

Approximately, 200 g of S109080 were milled using a centrifugal ball mill (Pulverisette, Fritsch GMBH, Germany) or with an apex mill (Model 314, Apex Construction Ltd, UK) equipped with a 152 μm screen. Table 1 gives a summary of the active batches used in the blending studies. Two of the three sections of S109080 milled using the Apex mill were allowed to recrystallise under different conditions (e.g. with and without pressure) to simulate storage of the active. Recrystallisation was confirmed prior to blending using techniques described below.

One of the sections of S109080 was blended immediately after milling to assess the impact of amorphous material on the blending characteristics of this active.

2.1.1. Preparation of amorphous and crystalline standards

A solution of xemilofiban with reaction by-products ($\sim$200 mg xemilofiban in $\sim$800 mg dimethylacetate) was diluted with acetylnitrile (670 ml) while mixing at ambient temperature. The solids that formed (presumed amorphous xemilofiban) were collected by filtration, washed with copious amounts of acetone, and dried under vacuum. This sample of xemilofiban exhibited a halo, characteristic of amorphous material, with powder X-ray diffraction (PXRD) and was non-birefringence by photomicroscopy using a cross polarised light source. This material was used as the amorphous standard.

Xemilofiban batch S109030 was used as the '100%' crystalline standard material. This batch of xemilofiban was not milled and gave no indication of any amorphous content by dynamic vapour sorption (DVS) analysis.

All other chemicals and reagents were HPLC grade and were used as received.

Table 1
Summary of xemilofiban active batches used in the blending study

Name	Milling equipment/conditions	Storage conditions after milling and prior to blending
Control	Batch S109080, Unmilled	Not milled
Ball milled	Above control, Ball milled at 200 rpm for 10 min	Stored after milling in a glass bottle at ambient conditions
Apex milled/ambient	Above control, Apex milled through 152 μm screen	Stored after milling in a glass bottle at ambient conditions
Apex milled/pressure	Above control, Apex milled through 152 μm screen	Stored after milling in a polythene bag under a 15 kg weight at ambient conditions
Apex milled/amorphous	Above control, Apex milled through 152 μm screen	Used immediately after milling in blending study

Note: the active was stored until the amorphous material generated through the milling process was no longer detectable using the techniques described in this paper. The storage time was between 2 and 3 months. The apex milled/amorphous batch however was blended immediately following the milling process.

2.2. Characterisation methods

2.2.1. DSC analysis

DSC analysis was performed using a TA 2920 (TA instruments, Surrey, UK). Samples (2–10 mg) were accurately weighed into an open aluminium pan and analysed over a temperature range of 40–250 °C using a heating rate of 5 °C/min. DSC analysis was performed on the recrystallised batches to confirm the correct polymorphic form of xemilofiban was present.

2.2.2. Dynamic vapour sorption (DVS) analysis

The moisture uptake studies were performed with a dynamic vapour sorption apparatus (DVS, Surface Measurement Systems, London, UK) at 25 °C. The apparatus consists of a Cahn microbalance housed inside a temperature-controlled cabinet. The humidity is controlled via switching valves, which control the flow of a dry gas (nitrogen) through a humidification stage. Samples (10–20 mg) were loaded onto one side of a twin pan balance, and the software programme controlled such that the sample was dried at 0% relative humidity (RH), and then raised in humidity steps of 10–95% RH following equilibration at each step.

2.2.3. Isothermal microcalorimetry (ITMC)

The heat flow studies were performed using a heat conduction microcalorimeter (TAM 2277, Thermometric AB, Jarfalla, Sweden), equipped with both standard ampoule calorimetric units and 20 ml vapour perfusion units. During the experiments the heat flow signal (dQ/dt in μW) is monitored as a function of time and by integrating the heat flow curve over a specific time, the heat (Q in J) evolved or absorbed can be obtained

In this study the isothermal microcalorimeter was used both to quantify the levels of amorphous material (Aso et al., 1995; Ahmed et al., 1996) and to measure the heats of adsorption of water vapour (Sheridan et al., 1995) on the recrystallised active samples.

2.2.3.1. Amorphous quantification. This study used the miniature humidity chamber technique (Angberg, 1995) where a sample is placed in a sealed ampoule under conditions which allow the transition to the crystalline state to take place.

Various predetermined amounts of amorphous standard were accurately weighed directly into glass ampoules and crystalline standard was added to bring the total weight of each to 1.50 ± 0.05 g. A vial of either water or a saturated salt solution ($MgCl_2$) was placed inside the glass ampoule and the ampoule crimp sealed to create a humidity chamber. An empty glass ampoule was used as a reference vessel. The sample and reference ampoules were temperature equilibrated for approximately 30 min within the ITMC, before being lowered into the measurement position.

Preliminary studies indicated that the amorphous standard required an atmosphere of 100% RH to recrystallise the amorphous content within the time frame of the experiment, whereas the amorphous material created via milling recrystallised at significantly lower humidity levels (53% RH, MgCl saturated solution). A lower relative humidity was used for the amorphous material created through milling, as recrystallisation could occur during the temperature equilibration period during which time no data is collected. This phenomena whereby different conditions are required to recrystallise amorphous material generated by different methods, e.g. milling versus quenching a melt etc., has been observed in house with other actives. It is thought that the amorphous material generated through milling recrystallises at a lower RH due to the existence of crystalline seeds in the milled batches. The specific heat of crystallisation should be independent of the RH used during the measurement (Sebhatu et al., 1994), and although the kinetics of recrystallisation might be affected this will not affect the quantification of the amorphous content.

2.2.3.2. Heats of adsorption of water vapour. The experiments were performed using a vapour perfusion cell, where the RH is controlled by mixing two different air streams (0 and 100% RH, respectively). By keeping the total flow rate constant, and varying the ratio of dry and saturated gas, any desired RH can be obtained within the ampoule.

Table 2
Composition of xemilofiban 10 mg powder blends

Material	% (w/w)	Theoretical weight
Xemilofiban HCl	5.5	110 g
Avicel® PH 302 section 1	44.5	890 g
Avicel® PH 302 section 2	44.5	890 g
Starch	4.0	80 g
Talc	1.0	20 g
Magnesium stearate	0.5	10 g
Totals	100.0	2 kg

Note: the Avicel® PH 302 is added to the blend in two sections.

Five hundred milligrams of powder was accurately weighed out into a 20 ml vapour perfusion ampoule and the vapour perfusion unit attached. The sample was exposed to 0% RH until a baseline had been established and then the RH was increased by steps of 10% every 3 h. The area under the exothermic responses was measured and used to prepare cumulative heats of adsorption plots for each milled active batch in duplicate.

The blank response for passing air of differing humidities through the empty sample cell was not measured in this study. Previous data had shown this response to be extremely constant and as this study was only using this technique to investigate differences between active batches, it was not deemed necessary to measure the blank response and subtract it from each of the measured responses. This study was used to investigate differences in the surface properties of the milled batches following recrystallisation of the amorphous content in an attempt to replicate the results from the characterisation study of the active batches used in the registration stability study.

2.2.4. Particle size analysis

Samples were analysed in the dry state using a laser light diffraction particle size analyser (Sympatec, Inc, Princeton, NJ). The diffracted light is captured by a 64-channel photodiode array detector, and Fraunhofer theory is used to calculate the sample's volume PSD from the energy distribution. Using a feed rate of 35%, approximately 1 g of sample was fed into the dispersion system. Dispersion of the particles was achieved with a pressure of 3 bar. The particle size data was generated in triplicate using an R3 (100 mm) lens, which has a working range of 0.5–175 μm.

2.2.5. Surface area analysis

The surface areas of the active samples were measured by nitrogen adsorption (Gemini II 2370, Micromeritics, USA) using a BET multipoint method. Prior to analysis the samples were degassed at 100 °C for between 2 and 4 h to remove any surface contaminants (e.g. moisture, adsorbed gases). Five replicates were analysed for each batch, the results of which were accepted provided the correlation coefficient was 0.999 or higher and the *C* value (BET constant) was between 40 and 80.

2.3. Blending studies

The composition of each blend is shown in Table 2. The registration stability batches were manufactured in a drum blender (45 kg) whereas in this laboratory study the blending was performed in a cube blender (2 kg). The batches were manufactured using the same procedure as was used for the registration stability batches.

2.3.1. Blend analysis

The blend was sampled in 20 different positions using a compartmental thief, the inserts of which gave approximately a unit dose (200 mg). The active was extracted with mechanical shaking for 30 min using 200 mls of a 50 mM potassium phosphate monobasic solution in water. A 1:5 dilution with the same extraction solvent was made and the solutions scanned from 200 to 350 nm with the maximum absorbance 271 nm recorded. The absorbance of a solution of 11 mg of xemilofiban reference sample in 1000 ml of 50 mM phosphate buffer at the same wavelength was used to quantify the samples, with an appropriate correction being made for the sample weight.

3. Results and discussion

3.1. Amorphous content of milled batches

The amorphous content of the milled active batches was assessed qualitatively using DVS moisture sorption analysis and quantitatively using isothermal microcalorimetry.

Fig. 1 shows a two cycle DVS moisture sorption profile for the unmilled active control and represents a typical moisture sorption profile for crystalline xemilofiban. The small amount of sorbed moisture ($< 0.3\%$ w/w at 95% RH), the absence of hysteresis, and the reversibility of the adsorption–desorption process confirms that the moisture is adsorbed at the crystal surface. The data shows the sample is reaching equilibration at each RH value and no physical changes (i.e. amorphous to crystalline transitions) are taking place.

Fig. 2 represents a typical moisture sorption profile for a milled batch of xemilofiban containing a small amount of amorphous material ($<$ 5%) analysed within 2 h of milling. In comparison to the unmilled batch, the milled active absorbs considerably more moisture at 50% RH (0.26% w/w compared with 0.11% w/w). At 60% RH the sample continues to absorb moisture until a moisture uptake of approximately 0.3% w/w is reached, at which point there is a sharp decrease in weight. At this point the absorbed moisture has reduced the glass transition temperature (Tg) of the amorphous xemilofiban below the operating temperature of the experiment. This sharp decrease corresponds to the expulsion of moisture as the amorphous xemilofiban recrystallises. In contrast to the unmilled batch there is a significant difference between the first and second sorption cycles. During the first cycle moisture is both adsorbed onto the surface and absorbed into the amorphous regions of the drug crystal, whereas in the second cycle moisture is only adsorbed onto the crystalline surface.

Fig. 3 shows the moisture sorption profiles for the xemilofiban active batches immediately after milling (the unmilled active batch is included for comparison). The DVS moisture sorption profiles indicate that milling has created amorphous regions within the active batches. All show an increase in moisture sorption compared with the unmilled batch, and in addition exhibit a characteristic expulsion of moisture above 50% RH. In

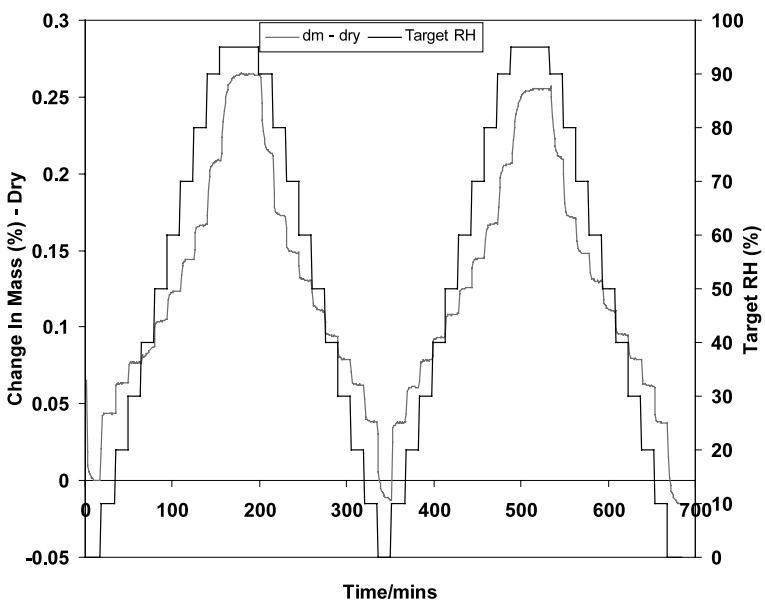

Fig. 1. Moisture sorption profile for xemilofiban active batch S109080.

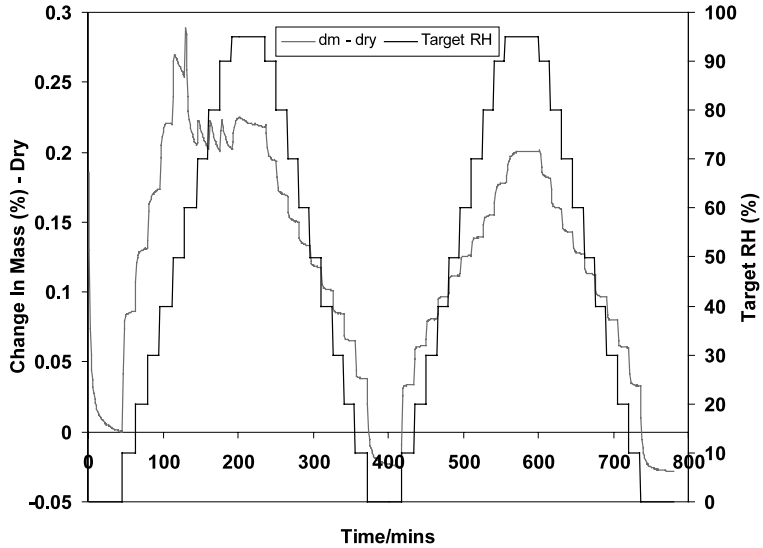

Fig. 2. Moisture sorption profile for xemilofiban active batch S109080 milled through a 152 μm screen on an apex mill.

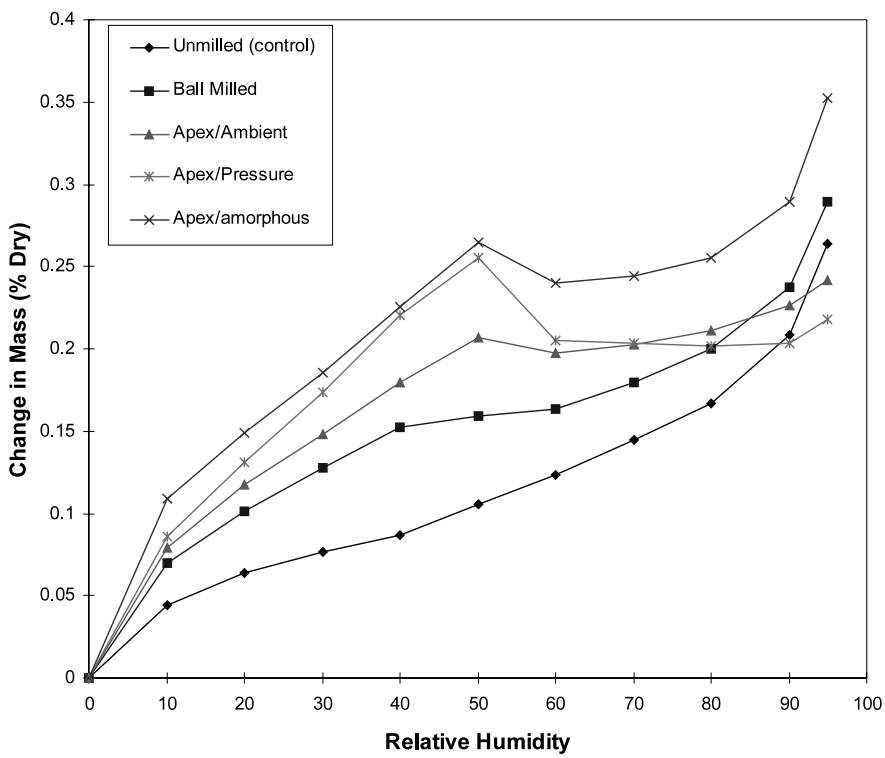

Fig. 3. Comparison of the moisture sorption profiles of milled xemilofiban active batches immediately after milling (control batch shown for comparison).

the case of the batch milled in a centrifugal ball mill this is difficult to detect in the mass versus RH plot, and although it can clearly be seen in the mass versus time plot, the amount of absorbed moisture expelled indicates that this type of milling has created lower levels of amorphous material compared with the apex mill.

The moisture sorption isotherms were not used to quantify the amount of amorphous material, as the total amount sorbed is a combination of moisture adsorbed onto the surface and absorbed into the amorphous regions. Variations in moisture uptake could be due to either differences in the amorphous content or the surface properties of the sample. Whilst the amount of adsorbed moisture is negligible compared with absorbed moisture in the 100% amorphous samples, for micronised active batches with relatively low levels of amorphous material ($< 5\%$), the difference in surface adsorbed moisture could lead to large errors in quantifying the levels of amorphous material.

Based on the amount of sorbed moisture and the magnitude of the expulsion of water vapour it was estimated that the amount of amorphous material in the active batches decreased in the following order: apex/amorphous > apex/pressure > apex/ambient > ball milled > unmilled.

A typical ITMC trace for the recrystallisation of a xemilofiban sample containing amorphous material is shown in Fig. 4. Essentially there is no response for approximately 20–25 h after which there is a large exothermic response; the area under this response represents the total heat of the recrystallisation process.

In this type of ITMC experiment, the positioning of the vapour generation site and powder both within the measuring cell results in only a small wetting response being recorded as the heat response from the generation of water vapour (endothermic) and it's sorption onto the powder (exothermic response) are nearly equal (Briggner et al., 1994). This is important as if the vapour was generated remote from the measuring site and passed over the sample, a large wetting event

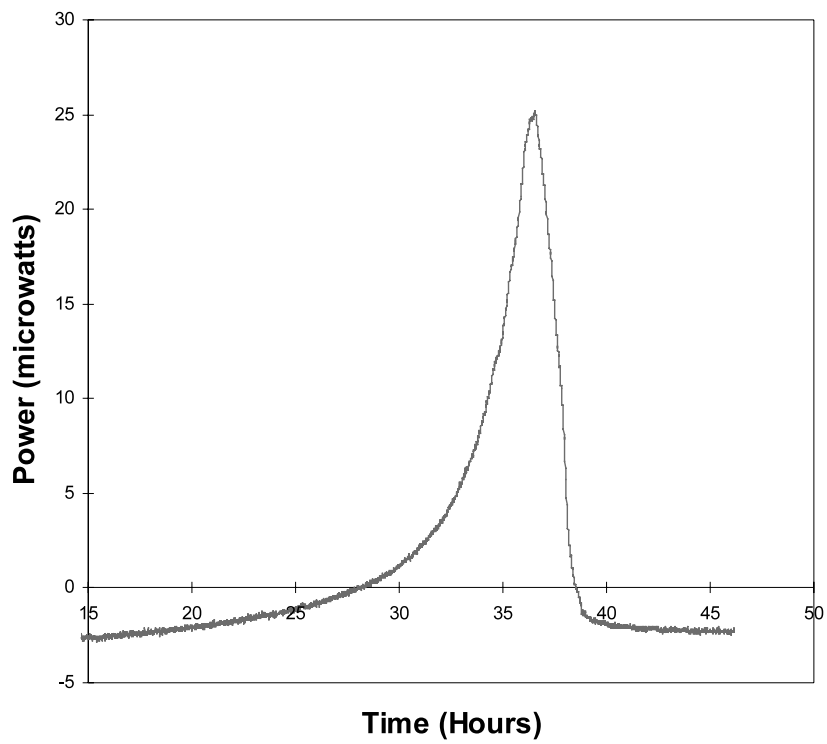

Fig. 4. Typical ITMC output of power as a function of time for a xemilofiban sample containing amorphous material.

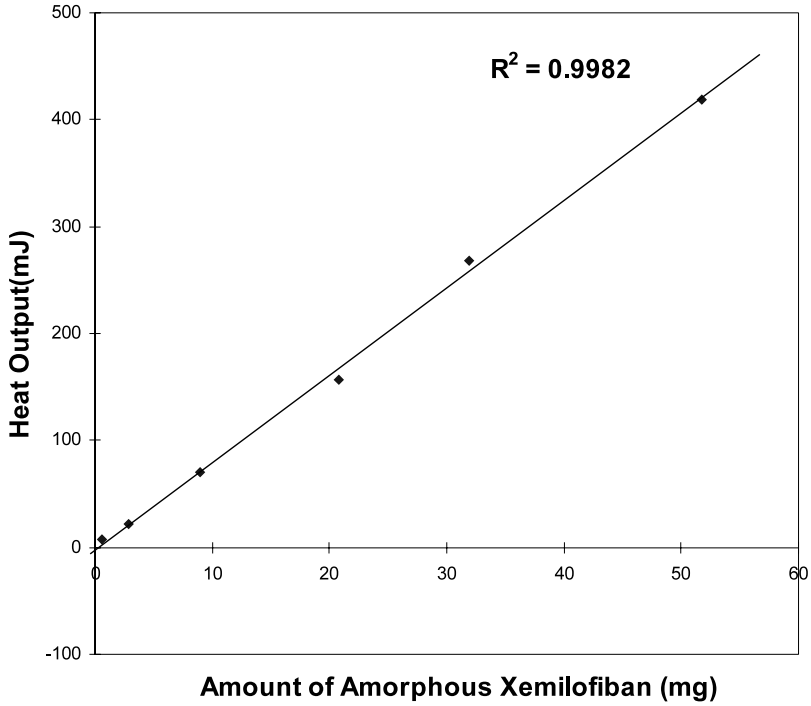

Fig. 5. Calibration graph for the detection of amorphous xemilofiban using an isothermal microcalorimeter.

would be detected which could possibly mask the recrystallisation event.

A standard graph was generated (Fig. 5) with the ITMC technique using mixtures of amorphous and crystalline standards prepared as described earlier. This graph was used for subsequent quantitative determinations of amorphous content.

The calibration graph was used to determine the amount of amorphous xemilofiban present in the milled active batches prior to allowing recrystallisation through storage. A summary of the DVS and ITMC results is shown in Table 3. The ITMC technique was being developed in parallel to this work and as such no data is available for ball milled batches.

The DVS and ITMC data both confirm the presence of small amounts of amorphous material ($< 5\%$) in the active batches following milling. The batches milled using an apex mill have an amorphous content ranging from 2.7 to 4.1% suggesting that the generation of amorphous material is extremely variable, as the same starting material and milling conditions were used.

3.2. Characterisation of active batches following recrystallisation of the amorphous material

Samples of milled material were tested every 2–3 weeks to determine whether recrystallisation

Table 3
Quantity of amorphous xemilofiban in control and milled batches

Xemilofiban batch	Amorphous xemilofiban detected by DVS	Quantity of amorphous xemilofiban by ITMC
Control	No	None
Ball milled prior to storage	Yes	Not available
Apex/ambient	Yes	2.7%***
Apex/pressure	Yes	4.1%
Apex/amorphous	Yes	3.6%

Note: ***sample analysed 6 days post milling, all other batches were analysed within 2 h of milling.

Table 4
Particle size analysis of milled (and recrystallised) and unmilled samples of xemilofiban batch S109080

	PSD (μm)		
	×10	×50	×90
Control batch	1.7	6.7	14.2
Ball milled batch	1.8	6.8	14.5
Apex milled/ambient	1.7	6.6	14.0
Apex milled/pressure	1.7	6.4	13.8

Note: the ×10, ×50 and ×90 values represent the 10% less than, 50% less than and 90% less than PSD points.

Table 5
Surface area analysis of xemilofiban batches

Active batch	Surface area (m^2/g) mean of five measurements	RSD of five measurements (%)
Control batch	2.6	6.5
Ball milled batch	3.0	6.6
Apex milled/ambient	2.4	5.1
Apex milled/pressure	2.6	5.1

was complete. Only when no evidence of amorphous material was confirmed by DVS and/or ITMC were the samples further characterised and then used in the blending studies.

The recrystallisation process occurred over a time period of approximately 2–3 months with the recrystallisation kinetics slowed by the relatively non aggressive environmental conditions (e.g. humidity and temperature) experienced during storage. By contrast, exposure of the milled active batches to a humidity level above 53% RH at 25 °C would be expected to recrystallise the amorphous material within a few hours.

The particle size data shown in Table 4 indicates that milling and any subsequent recrystallisation of amorphous regions has not reduced the particle size of the drug crystal. This data confirmed previous milling experience with this active, which indicated that the size reduction process only serves to break down large agglomerates that were formed during the drying process and that the primary particles were extremely resistant to further size reduction.

The results from surface area (BET) analysis (Table 5) indicates that milling followed by recrystallisation did not significantly change the surface area. This technique is extremely sensitive to subtle changes in the particle sizes of powders below 10 μm, and together with the particle size data shown in Table 3 gives conclusive evidence that milling and subsequent recrystallisation did not significantly alter the particle size of the drug crystals.

Fig. 6 shows the moisture sorption profiles of the xemilofiban batches milled in this laboratory study, after the amorphous material had recrystallised. In comparison to the unmilled active batch, the milled batches all sorbed more moisture across the entire RH range even though there it has been shown that there is no significant difference in their surface areas. The apex milled/pressure batch showed a significantly higher moisture uptake above 80% RH compared with all the other batches.

The heats of adsorption of water vapour for the milled xemilofiban batches is shown in Fig. 7. This technique offers a very sensitive and extremely reproducible method for probing the surface of a powder as subtle variations in surface composition, in terms of the chemical nature and location of chemical groups, is often what gives rise to lot-to-lot variations in raw materials encountered within pharmaceutical systems (Zografi, 1981). Using the vapour perfusion units the adsorption of different vapour states can be measured over a range of partial pressures with the assumption that the extent of adsorption of a particular gas is related to the interaction energy, which in turns reflects the surface energetics.

The data in Fig. 7 shows a difference between the unmilled and milled xemilofiban batches following recrystallisation of the amorphous regions. The error bars on Fig. 7 are nearly within the symbols on each plot indicating that this technique gives a reliable indication of the powder's surface energetics. The heat flow curve for a milled active batch, S109050, which failed the blend content uniformity criteria during the man-

ufacture of the registration stability tablets has been included for comparison. The active batches milled for this laboratory study have heats of adsorption intermediate to the unmilled batch and batch S109050, suggesting that milling has altered the surface energetics.

The characterisation data indicates that although the amorphous regions have recrystallised

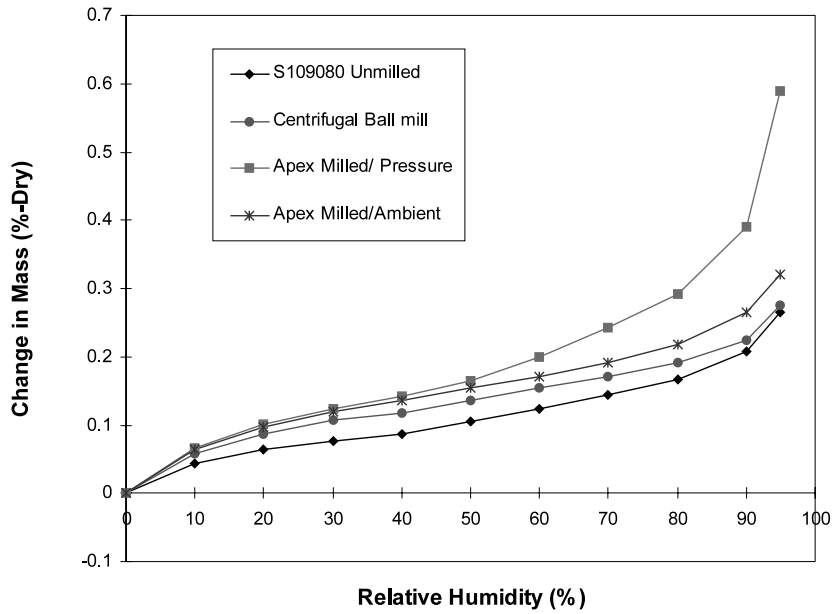

Fig. 6. Comparison of the moisture sorption profiles of milled xemilofiban active batches after recrystallisation (unmilled batch shown for comparison).

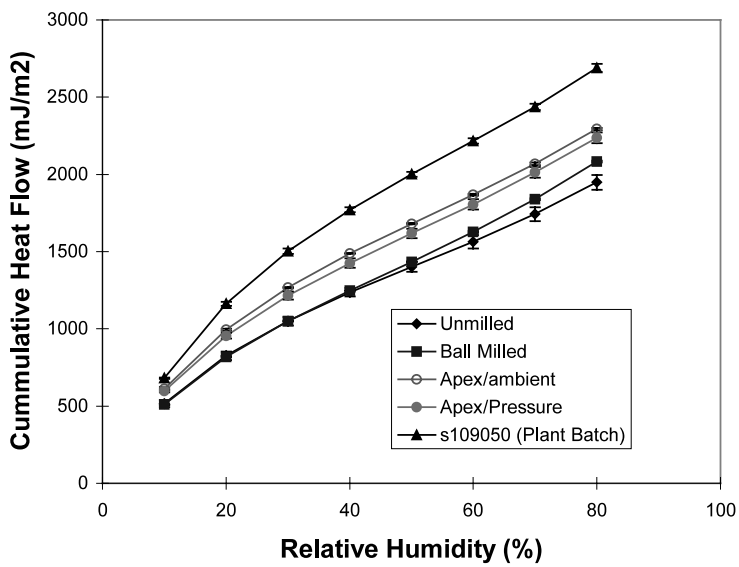

Fig. 7. Heats of adsorption of water vapour determined by isothermal microcalorimetry for milled xemilofiban batches after recrystallisation.

Table 6
Blend content uniformity results for xemilofiban 10 mg blends before lubrication with magnesium stearate

	Content uniformity (%)			
	Mean	RSD	Max	Min
Control	100.0	1.3	102.8	98.1
Ball milled	99.4	3.1	108.0	95.0
Apex milled/ambient	98.4	2.9	106.8	96.5
Apex milled/pressure	97.3**	6.3	106.2	72.8
Apex milled/amorphous	101.7	8.9	138.8	97.9

Note: **a number of lumps were detected on the surface of the blend. One was isolated, analysed and found to have a xemilofiban content of 134% of the theoretical content.

Table 7
Blend content uniformity results for xemilofiban 10 mg blends after lubrication with magnesium stearate

Batch	Mean	RSD	Max	Min
Control	100.0	1.4	104.1	97.6
Ball milled	97.7	2.5	101.5	94.3
Apex milled/ambient	99.5	3.5	110.8	96.4
Apex milled/pressure	98.5	0.6	99.6	96.6
Apex milled/amorphous	99.9	0.6	100.8	98.9

to their original crystalline form, there are subtle differences in the surface properties between the unmilled and milled/recrystallised xemilofiban batches as was observed during the characterisation of the active batches used in the manufacture of the registration stability tablet batches.

3.3. Blending studies results

The effect of milling on the processing behaviour of xemilofiban active batches can be seen from the data in Table 6. Without exception, when compared with the unmilled control batch, milling of xemilofiban active batches reduced the uniformity of subsequent blends produced from those batches, even if any amorphous content created during milling is first allowed to recrystallise.

The unmilled batch gave excellent blend content uniformity with a mean active content of 100.0% of theoretical and a blend RSD of 1.3%. This blend content uniformity data is typical for unmilled xemilofiban active batches used in the manufacture of xemilofiban tablets.

In contrast to the unmilled active batch, the apex milled/pressure batch had a mean active content of 97.3% with an RSD of 6.34%. In addition to the poor blend content uniformity results there were several aggregates visible on the surface of the blend. One of these aggregates was removed and found to have a xemilofiban content of 134% of theoretical concentration. These aggregates also appeared in the 'problem' registration batches.

The ball milled and apex milled/ambient active batches had mean active content values of 99.4 and 98.4%, respectively, with blend RSD values of 3.1 and 2.9%, respectively. Although these batches meet the USP blend content uniformity criteria, both have significantly higher blend RSD results when compared with the unmilled active batch

The apex mill/amorphous batch had a mean active content of 101.7% with an RSD of 8.9%. It is well documented throughout the literature that high energy processes such as milling can affect the surface properties of solids (Buckton, 1997). Amorphous material exists in a high energy state and therefore behaves in a different manner to its crystalline counterpart, influencing interactions between surfaces, such as cohesiveness and adhesion between the powder and other phases, and as such is capable of changing the processing behaviour of a powder. The presence of amorphous material within this milled active batch has significantly affected its blending properties.

The blend content uniformity results after lubrication are shown in Table 7. The unmilled active batch again gave excellent blend content uniformity results after lubrication with a mean active content of 100.0% and a blend RSD of 1.4% compared with a mean active content of 100.0% and a blend RSD of 1.3% before lubrication. These results support the excellent blending properties of the unmilled xemilofiban active batch, as well as the validity of both the sampling plan and analytical analysis.

The data in Table 7 indicates that the addition of magnesium stearate has had a remarkable affect on the blending characteristics of the milled active batches that had previously failed the blend

content uniformity criteria. The blend RSD's were reduced from 8.9 and 6.3 to 0.6% for the apex milled/amorphous and apex milled/pressure batches, respectively.

During the manufacture of the registration stability batches, this phenomena was also observed where with one milled active batch the blend RSD was reduced from 15.3 to 3.8% following lubrication with magnesium stearate. The addition of magnesium stearate had little or no effect on those blends that had acceptable blend content uniformity prior to lubrication with magnesium stearate. It has previously been reported in the literature (Staniforth, 1982) that magnesium stearate particles can alter the electrostatic interactions between adhered particles. The dramatic improvement in blend uniformity following lubrication with magnesium stearate also suggests that milling had impacted the surface properties.

4. Conclusions

It has been suggested that the most important cause of variability in powder properties may be due to changes in their surface properties (Buckton and Darcy, 1995). In this study the blending characteristics of an active with amorphous material before and after recrystallisation has been studied. It was observed that even a small amount of disorder at the surface of an active had an impact on the blending characteristics of a direct compression formulation. Furthermore when this amorphous material recrystallised, the powder displayed different physical properties and blending characteristics to its original unmilled state. One explanation for this phenomena is that the amorphous material, which is likely to be predominantly located on the surface, recrystallised to a different polymorphic form of the drug changing its physical properties and blending characteristics. DSC testing was performed on each milled sample to confirm the correct polymorphic form was present. However, given that the amount of amorphous material in a milled batch was less than 10%, it is possible that the amount was below the limit of detection for this technique.

The work in this paper emphasises the need to develop techniques to quantify relatively low amounts of amorphous material ($< 5\%$) during the early stages of the compound's development cycle such that the impact on the processing behaviour, stability, and bioavailability of the formulation can be fully investigated and understood.

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