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The Effect of Spray-Drying Feed Temperature and Subsequent Crystallization Conditions on the Physical Form of Lactose

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INTRODUCTION

Spray-drying is known to produce predominantly amorphous material because of rapid solidification.[1] The detection and control of the amorphous portion of powdered material is of utmost importance, as different physical forms of materials have different physicochemical properties that give rise to significant differences in functionality when used in dosage forms. The influence of spray-drier feed concentration on the degree of crystallinity and the crystal form of lactose (β-lactose, anhydrous α-lactose, α-lactose monohydrate) has been described previously.[2] It is known[2] that the spray-drying process can be made to produce completely amorphous lactose particles. Furthermore, it is clear that the amorphous form is unstable and that it will revert to the crystalline form. In this work, the impact of feed temperature variation and the conditions used to induce crystallization have been investigated, with respect to the physical form that is produced.

MATERIALS AND METHODS

Materials

α-Lactose monohydrate (SmithKline Beecham, batch E0013) was used to prepare the spray-dried samples. β-lactose (Sigma Chemicals) was used as a reference material.

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Lactose solutions (20 g/100 mL) in distilled water were prepared and equilibrated at 25, 30, 40, and 50°C, then spray-dried using a Buchi 190 spray drier. The spray-drying variables were kept constant and were as described by Chidavaenzi et al,[2] except for the feed rate, which was varied for each feed temperature to minimize fluctuations in the outlet temperature. The materials were collected and immediately desiccated over silica gel.

Crystallization of amorphous samples

Each sample was accurately weighed (25- or 100-mg samples) in a 3-mL glass ampule. Each ampule had a small tube containing a saturated solution to give the desired relative humidity (RH) at 25°C ($Mg(NO_3)_2$ 54% RH; NaCl 75% RH; water 100% RH). The ampules were sealed and temperature-equilibrated for 30 minutes before being lowered into the measuring position of an isothermal microcalorimeter (Thermal Activity Monitor, Thermometric, Sweden). A reference experiment was undertaken by sealing an identical ampule and salt solution without powder present. The use of a freshly sealed blank ampule minimizes heat effects due to relaxation of the rubber stopper of the ampule, evaporation from the salt solution, and the baseline drift that is associated with environmental heat changes.[3] As soon as the crystallization response returned to baseline, the experiments were terminated and the saturated solution was removed. The anomeric content of the sample was then determined by use of gas chromatography following the method of Dwivedi and Mitchell.[4] To derivatize the samples, 1 mg of solid lactose was dissolved in 2.25 mL of trimethylsilylimidazole (22%), dimethyl sulfoxide (19.5%), and pyridine (58.5%). The samples were vortexed for 2 min

Table 1. α- and β-Lactose Composition of the Feed Solutions and the Spray-Dried Products

Feed Temperature (°C)	% α-Lactose in Solution*	% β-Lactose in Solution*	% α-Lactose in Amorphous Solid†	% β-Lactose in Amorphous Solid‡
25	40	60	63 (0.4)	37
30	41	59	59 (0.4)	41
40	43	57	48 (0.6)	52
50	44	56	43 (1.0)	57

*Data from Dwivedi and Mitchell.[4]
†Data determined from GC (n = 4).
‡Determined as 100%.

utes and stored at room temperature. Aliquots (2 μL) were injected directly into the gas chromatography (GC) column (Carlo Erba HRGC 5300, CP-sil 43CB column flame ionization detector, column temperature 200°C, injection port and detector 250°C).

Powder x-ray diffraction

Where appropriate, samples were also assessed using powder x-ray diffraction Cu-K-α-radiation, 40 kV, 30 mA, in an atmosphere of less than 20% RH at room temperature. Diffraction peaks at 10.5° and 12.6° are characteristic of crystalline β- and α-lactose monohydrate, respectively.

RESULTS AND DISCUSSION

Nature of the spray-dried material

The spray-dried material (at each feed temperature) was found to crystallize in the isothermal microcalorimeter with an area under the curve of about 50 J/g (with slight variation depending on RH and mass used), which is in keeping with the observation of Briggner et al.[3] The powder x-ray diffraction pattern for the spray-dried material (data not shown) was in all cases featureless and indicated the presence of an amorphous form.

The α- and β-lactose composition of lactose solutions at different temperatures is known[4] and is shown for the feed temperatures used in this study in **Table 1**. Also in **Table 1** are the values determined for the α- and β-lactose composition of the spray-dried product (determined using the GC method). It can be seen from **Table 1** that the α- and β-lactose composition for the feed solutions would be expected to vary slightly, with the higher temperatures giving a slightly greater proportion of α-lactose in the feed solution. It may have been expected that the anomeric content of the spray-dried products would reflect that of the input solution; however, there are significant differences in that the samples from low-temperature feed solutions have undergone substantial mutarotation during the spray-drying process. For example, the 25°C feed started at a ratio of 40:60 α:β-lactose in solution but was 63:37 α:β-lactose in the spray-dried amorphous product. At high feed temperatures, however, the mutarotation did not occur; for example, 50°C feed had a ratio of α:β-lactose of 44:56 in solution and the same in the amorphous solid (within experimental error). It must be assumed that the solution with high feed temperature dried slightly more rapidly and thus had less time to mutarotate during the drying process.

Nature of the crystallized form

A comparison of the α- and β-lactose composition of the spray-dried products and the resultant crystalline material that was generated by exposure of 20-mg samples to 54% RH is shown in **Table 2**. It can be seen that the crystallized samples have essentially the same α: β content irrespective of the original spray-dried product composition. This was also the case when 100 mg of sample was crystallized at 54% RH (there was no difference in the composition of the crystalline material with changes in sample mass when 54% RH was used to induce crystallization). In each case, the anomeric content of the sample was determined at the end of the calorimetric crystallization response, so that only changes that occurred during the crystallization itself were recorded. It is known that storage of β-lactose at elevated humidity will result in a mutarotation and a slow (over many days) calorimetric heat flow[5]; as mentioned above, this post-crystallization mutarotation was not recorded on this occasion because of termination of the process as the crystallization peak returned to baseline. The time needed to cause 100 mg of powder to crystallize in the calorimeter at 54% RH was much longer than that for 20 mg at 54%

Table 2. α- and β-Lactose Composition of the Spray-Dried Amorphous Products and of the Crystallized Material When 20 mg Was Exposed to 54% Relative Humidity

Feed Temperature (°C)	% α-Lactose in Solution*	% β-Lactose in Solution*	% α-Lactose in Amorphous Solid†	% β-Lactose in Amorphous Solid‡
25	40	60	63 (0.4)	37
30	41	59	59 (0.4)	41
40	43	57	48 (0.6)	52
50	44	56	43 (1.0)	57

RH (data not shown). The 100-mg samples had a lag time of more than 20 hours prior to crystallization, compared with just over 6 hours for the 20-mg samples. However, despite the different lag times, the samples had the same anomeric content at the end of the crystallization process. This indicates that the mutarotation occurred during the crystallization, not during the lag phase prior to crystallization. The lag before crystallization is a consequence of the slow diffusion of water vapor into the powder mass; the larger mass requires more water before 1 region has a sufficiently low glass transition temperature to allow crystallization to begin. It was also seen (**Figure 1**) that the crystallization peaks for the higher feed temperatures had a slower onset and had a distinct tail. It has been speculated previously (eg, Sebhatu et al[1]) that this tail is due to mutarotation; given that the tail is absent for the low feed temperature samples (which do not mutarotate), it can be concluded that mutarotation does occur during the crystallization process and gives rise to the changed shape of the response.

When the samples were crystallized using 75% RH, the anomeric ratio was different from that discussed above (54% RH). It can be seen from **Table 3** that the extent of mutarotation was lower at 75% than at 54% RH (**Tables 3** and **2**, respectively) when 20-mg samples were studied but was greater at 75% than 54% RH when 100-mg samples were used (**Table 3**). The 20-mg samples crystallized very rapidly at 75% RH (around 1-2 hours, **Figure 2**), and there was no evidence of the tailing that was seen in **Figure 1** for samples crystallized at lower RH. With the 100-mg sample at 75% RH, mutarotation was greater than at 54% RH, as there was a combination of time and higher RH, both of which encourage mutarotation to proceed. In **Table 4**, the anomeric ratios for samples crystallized at 100% RH are shown. Here, the mutarotation was substantial for the 20-mg sample; despite the rapid process, the water content must have been sufficiently great to allow mutarotation. For the 100-mg 100% RH sample, the mutarotation was almost complete.

CONCLUSION

Automated flow-through or programmed dissolution procedure with USP apparatus II and III was developed and proven to be suitable for in vitro CODES™ evaluation. Relatively speaking, the reciprocating cylinder method was demonstrated to be preferable. This study has addressed the effects of both instrument parameters and formulation variables on drug release profiles from APAP CODES™ products. Briefly, under a certain level of Eudragit E coating (eg, 8%), the reciprocation speed was a major factor in affecting the drug release rate in contrast to the paddle speed; the bottom screen mesh played a lesser role. By comparison, the reciprocating cylinder at appropriately lower dip speeds (eg, 5 dpm) can give a release profile close or equivalent to that of the paddle at 100 rpm. This may help define a starting point in future dissolution method development for assessing the performance of controlled or extended release drug products. Detailed research results with APAP CODES™ formulation development and in vitro/in vivo correlation will be addressed in a separate paper. The properties of the amorphous form of lactose are influenced by the processing conditions during spray-drying. Notably (**Figures 1** and **2**), the high-feed temperature materials have a longer lag time before crystallization onset. The feed solutions were indeed solutions, but some nucleation sites may remain when the feed temperature is lower. Alternatively, the higher percentage of β -lactose in the amorphous product for high-feed temperature material (**Table 1**) may slow the onset of crystallization (maybe because α-monohydrate would be the favored form in the humid environments that give rise to crystallization).

The anomeric content of the amorphous form does not simply reflect that of the feed solution. There is signify-

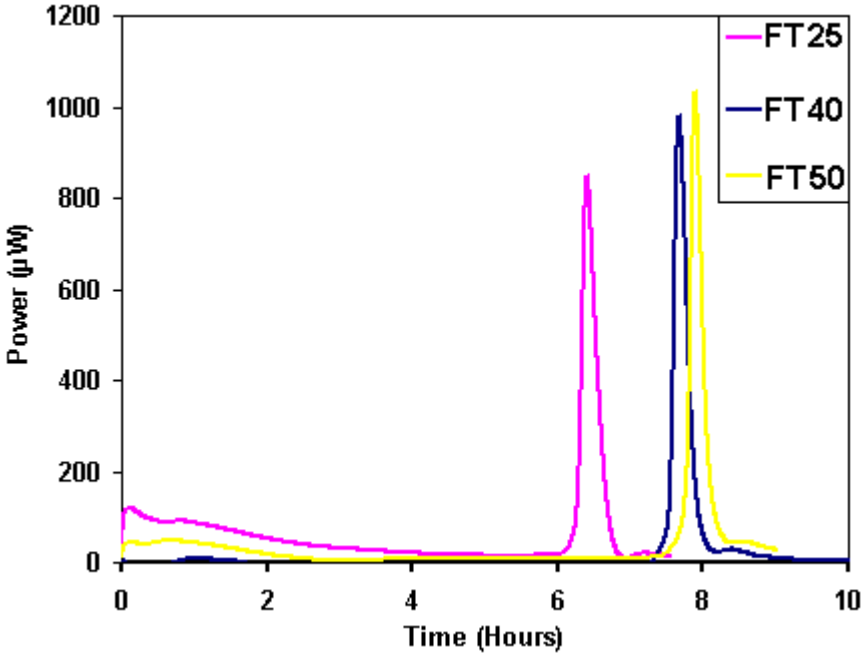

Figure 1. Responses from the isothermal microcalorimeter for the crystallization of 20 mg of sample at 54% RH. Pink = 25 °C feed temperature, Blue = 40 °C feed temperature and Yellow = 50 °C feed temperature.

Table 3. α- and β-Lactose Composition of the Spray-Dried Amorphous Products and of the Crystallized Material When 20 mg and 100 mg Was Exposed to 75% Relative Humidity

Feed Temperature (°C)	% α-Lactose in Crystalline Solid (20 mg)	% β-Lactose in Crystalline Solid (20 mg)	% α-Lactose in Crystalline Solid (100 mg)	% β-Lactose in Crystalline Solid (100 mg)
25	64 (0.6)	36	58 (1.4)	42
30	63 (0.5)	37	73 (1.7)	27
40	56 (0.5)	44	74 (0.5)	26
50	55 (0.4)	45	71 (0.6)	29

cant conversion during processing, but surprisingly not to yield similar final products (**Table 1**).

When crystallization was carried out at 54% RH, the crystalline product showed mutarotation from the range of anomeric contents of the amorphous form to all yield very similar ratios of α: β (approximately 63:37). During crystallization at 75% RH, mutarotation was greatly affected by sample mass, being much greater for the 100-mg than for the 20-mg sample, presumably because of a combination of the slower process and the higher water quantity present. This trend was extended for exposure to 100% RH, where mutarotation was almost complete for the higher sample mass.

The overall conclusion is that the transformation between the different physical forms of lactose is a complex process. To obtain reproducible material from any process, one must carefully consider the environment to which the sample was exposed as well as the mass of the material that was stored.

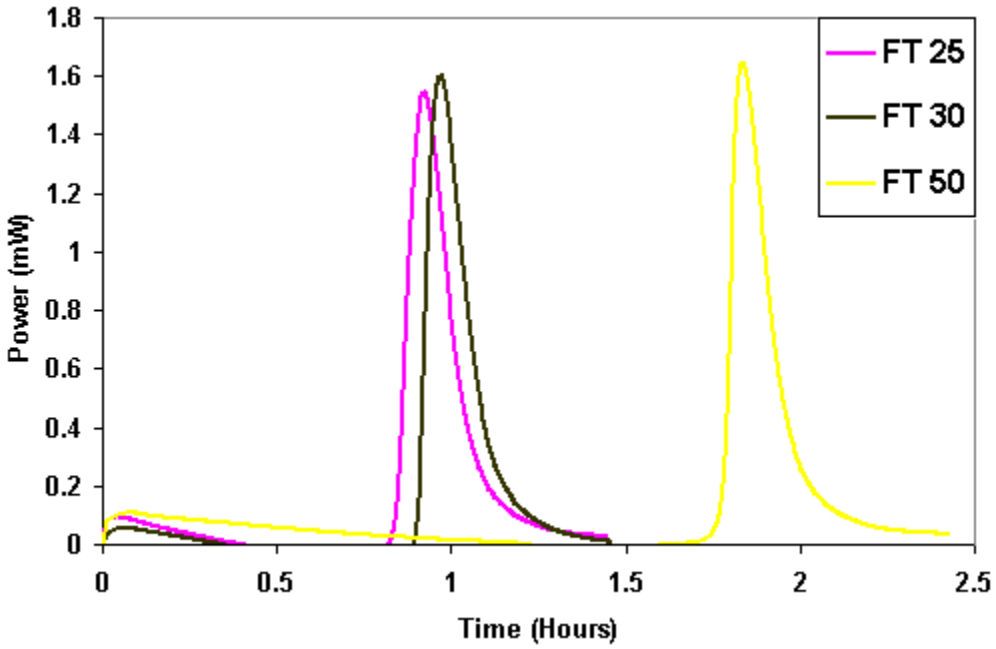

Figure 2. Responses from the isothermal microcalorimeter for the crystallization of 20 mg of sample at 54% RH. Pink = 25 °C feed temperature, Blue = 40 °C feed temperature and Yellow = 50 °C feed temperature.

Table 4. α- and β-Lactose Composition of the Spray-Dried Amorphous Products and of the Crystallized Material When 20 mg and 100 mg Was Exposed to 100% Relative Humidity

Feed Temperature (°C)	% α-Lactose in Crystalline Solid (20 mg)	% β-Lactose in Crystalline Solid (20 mg)	% α-Lactose in Crystalline Solid (100 mg)	% β-Lactose in Crystalline Solid (100 mg)
25	64 (0.6)	36	58 (1.4)	42
30	63 (0.5)	37	73 (1.7)	27
40	56 (0.5)	44	74 (0.5)	26
50	55 (0.4)	45	71 (0.6)	29

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