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DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY
Vol. 28, No. 8, pp. 949–955, 2002

RESEARCH PAPER

Effects of Ethanol to Water Ratio in Feed Solution on the Crystallinity of Spray-Dried Lactose

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ABSTRACT

In the present study, the effects of ethanol to water ratio in feed solution on the physical properties of spray-dried α-lactose monohydrate were evaluated. Crystallinity of the spray-dried lactose was determined by isothermal microcalorimetry (IMC) and by differential scanning calorimetry (DSC). Water content of the spray-dried lactose was determined by thermogravimetric analysis and the surface area was evaluated by Brunauer, Emmett, and Teller (BET) method. The crystallinity of spray-dried lactose varied from 0% to 100%, depending on the ratio of ethanol to water in the feed solution. Lactose spray dried from pure ethanol was 100% crystalline and contained hydrate water. Lactose spray dried from pure water was 100% amorphous. The feed solution substantially affected the ratio of surface water to hydrate water, as the content of surface water increased and hydrate water decreased, while the crystallinity of spray-dried lactose decreased. Surface area of the spray-dried lactose increased as a function of amorphous content.

Key Words: *Spray drying; Lactose; Crystallinity*

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DOI: 10.1081/DDC-120006427
0363-9045 (Print); 1520-5762 (Online)

INTRODUCTION

Spray drying is widely used in the pharmaceutical industry; e.g., in the preparation of spherical particles of drugs and excipients, granulation, microencapsulation, and complex formation.[1] Typically, a polymorphic change from a crystalline form to an amorphous form occurs during spray drying.[1–3] Amorphous forms of a drug may be useful in order to increase the dissolution rate of poorly soluble drugs.[4] On the other hand, conversion of a crystalline form into an amorphous form may be harmful as amorphous materials can decrease the physical and chemical stability of a product.[5,6] For example, highly crystalline drugs and excipients are required to formulate stable inhalation powders.[7,8]

The concentration of lactose in feed material has been demonstrated to affect the amorphous content of spray-dried lactose.[9,10] When water is used as feed solution, amorphicity of the spray-dried lactose has been shown to decrease from 100% to 82% when the lactose concentration in water is increased from 0.1 g/mL to 0.4 g/mL.[10] A highly crystalline form of lactose has been produced by spray drying while simultaneously optimizing the concentration of lactose in the feed material via inlet–outlet air temperatures and feed flow rate.[9] The aim of the present study was to investigate the effect of the ethanol to water ratio in feed solution on the crystallinity of spray-dried α-lactose monohydrate.

MATERIALS AND METHODS

Materials

Alpha-lactose monohydrate (Mesh 325) (Focus Inhalation Oy, Turku, Finland) was used to prepare the spray-dried samples because it is employed frequently as an excipient in the pharmaceutical industry. Distilled water and ethanol (Aa, Primalco, Rajamäki, Finland) were used to prepare the feed samples.

Spray Drying

The ratio of ethanol to water in the feed solution varied between 0:100 and 100:0. A 15% (w/w) lactose suspension or solution was spray dried with a Büchi Mini-Spray Drier 190 (Büchi Laboratorium-Technic AG, Flawil, Switzerland). The diameter of the nozzle was 0.7 mm. Lactose was mixed gently in the ethanol–water solution in a beaker equipped with magnetic stirrer for 5 min at room temperature (ca. 20°C) before spray drying. The spray-drying variables were kept constant (Table 1). The only exception was that lactose was spray-dried from pure distilled water (0% ethanol) at an inlet temperature of 160°C and an outlet temperature of 110°C. In that case, the higher outlet and inlet temperatures were needed because the boiling point of water is higher than that of ethanol. The spray-dried samples were packed into tightly closed plastic bottles and stored in a silica desiccator (ca. 20°C and <5% relative humidity, RH) prior to the studies.

Table 1

Parameters Used in Spray Drying Lactose Samples

Parameters	Controls
Air flow rate (dial setting)	15
Outlet temperature (°C)	72–80[a]
Inlet temperature (°C)	106–108[a]
Heating rate (dial setting)	7
Atomizer air flow rate (NormL/hr)	700
Feed rate (mL/min)	5

[a]Lactose was spray dried from water (0% ethanol) at an outlet temperature of 110°C and an inlet temperature of 160°C.

Isothermal Microcalorimetry Measurements (IMC)

The degree of amorphous lactose was measured using an isothermal heat-conduction microcalorimeter TAM 2277 (Thermometric AB, Järfälla, Sweden) at 25°C. Measurements were performed within 1–2 weeks after spray drying. The heat flow curves were monitored as a function of time. By integrating the heat flow curve over a specific time interval, the cumulative heat was obtained. Exothermic signals are given positive values in this article. The miniature humidity chamber technique[11,12] was employed to detect the thermal response for the recrystallization of amorphous lactose. The extent of heat evolution was considered directly to relate to the degree of amorphicity. During the measurement, the sample was recrystallized because of moisture absorbed from the saturated salt solution (ca. 54% RH), which was included in the hermetically sealed 3 mL glass ampoule as a desiccant, together with the sample. After spray drying the samples were prestored in a

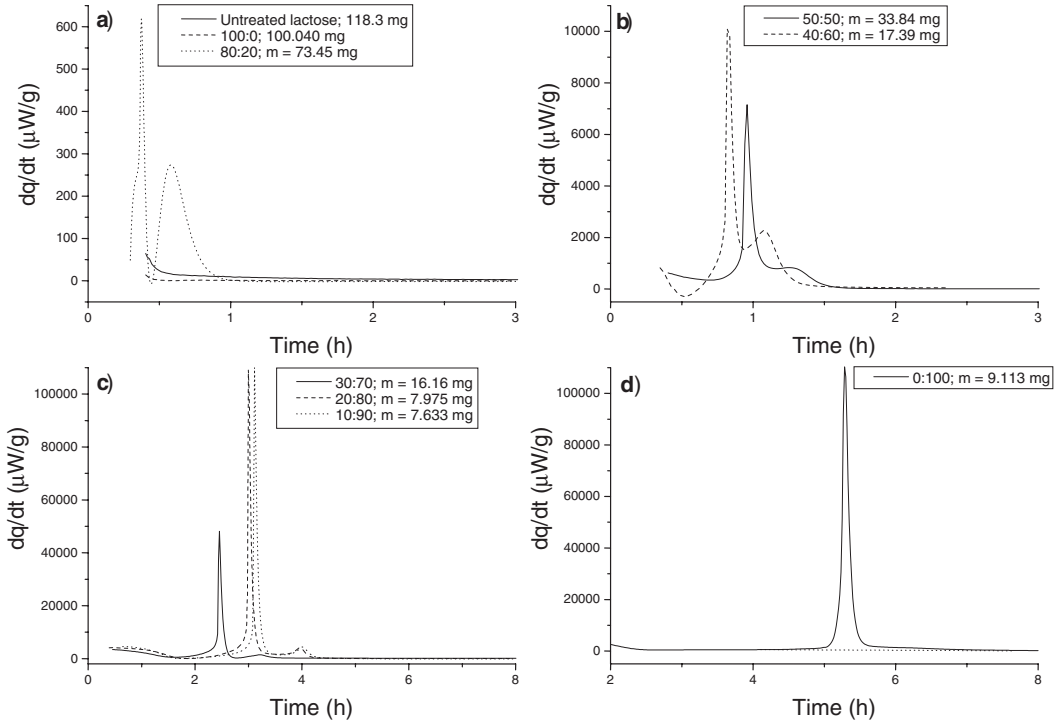

Figure 1. Typical microcalorimetric heat flow curves for the recrystallization of the lactose samples spray dried from various ethanol:water mixtures, using the miniature humidity chamber technique (54% RH, 25°C). The ratios shown (a–d) indicate the ethanol:water ratio. The dotted line in (d) represents the baseline for the recrystallization process.

silica desiccator (<5%) at room temperature (ca. 20°C), and accurately weigh (6–120 mg) just prior to the measurements. After preparation, the samples and identical reference ampoules containing no lactose were immediately placed in the equilibrium position of the TAM for 15 min prior to being lowered into the measuring position. The lactose sample that was spray dried from pure water was regarded as being totally amorphous (100%), as x-ray diffraction studies showed only diffuse scattering with no characteristic reflections of crystallinity in the resulting diffractogram. Each spray-dried lactose batch was measured in duplicate. The corresponding heat (59.5 J/g) for the recrystallization process (the area between the dotted and solid line in Fig. 1d) was taken as the reference value in calculations of amorphicity for the other samples (Fig. 1).

Differential Scanning Calorimetry (DSC)

Analyses were made with a Perkin-Elmer Pyris 1 differential scanning calorimeter (Perkin-Elmer, Norwalk, CT, USA). Pyris 1 was controlled by personal computer with Pyris software for Windows version 3.04. Temperature calibration was accomplished by a two-point calibration, using indium and tin as standards and enthalpy calibration using indium as the standard.

Measurements were made under a nitrogen flow rate of 50 mL/min in perforated Perkin-Elmer aluminum pans. The sample weights were between 5 and 10 mg, the heating rate was 2°C/min, and the temperature range 30–350°C. The thermograms of the samples containing amorphous lactose had a clear exothermic peak between 140–169°C due to crystallization of amorphous lactose. The heat (−102 J/g) for the recrystallization process of a freshly prepared lactose sample that was spray dried from pure water (100% amorphous lactose) was taken as the reference value in calculations of amorphicity for the other samples. The sample of 100% amorphous lactose was fresh, but the other spray-dried samples had been stored for several months in a silica desiccator (<5% RH) at room temperature (ca. 20°C) before DSC measurements.

Thermal Gravimetry (TG)

The TG measurements were made with a Perkin-Elmer configuration TGA 7, which was controlled by a TAC 7/DX controller and personal computer with Pyris Thermal Analysis System software version 3.52. Temperature calibration was accomplished by four thermomagnetic substances: alumel, nickel, nicoseal, and perkalloy.

Measurements were made in platinum pans under a nitrogen flow rate of 50 mL/min. The sample weights were between 5 and 10 mg, and the temperature range was 30–200°C. Heating rates of 20, 10, 5, 2, and 0.5°C/min were tested. A heating rate of 2°C/min was used in the measurements. The lactose sample was assumed to contain 100% α-lactose monohydrate when the sample contained 5.2% w/w hydrate water. When the sample contained less than 5.2% w/w hydrate water, the amount of lactose in the form of monohydrate as a percentage of the total lactose was calculated as follows: [hydrate water % (w/w) in the sample/5.2% (w/w)] × 100%. The 100% amorphous lactose was fresh but the other spray-dried samples had been stored for several months in a silica desiccator (<5% RH) at room temperature (ca. 20°C) before TG measurements.

Surface Area Measurement of Powders

The specific surface areas of samples were measured with a FlowSorb 2300 (Micromeritics, Norcross, GA) by determining the quantity of gas adsorbed as a single layer of molecules on a sample. The gas was composed of 30% nitrogen and 70% helium. Samples were stored in a vacuum silica desiccator (<5% RH) at room temperature (ca. 20°C) before measurements.

Scanning Electron Microscopy (SEM)

Particle morphology and shape were evaluated with a scanning electron microscope (Jeol JSM-35, Tokyo, Japan). Samples were coated with gold under vacuum (Sputter Coater II-E 5100, Polaron Equipment, UK). All micrographs were taken at an acceleration voltage of 15 kV.

Statistical Analysis

Statistical comparisons were made using the non-parametric Kruskal–Wallis test and the Games–Howell's multiple range test (SPSS® software). The level of significance was taken as $p < 0.05$.

RESULTS AND DISCUSSION

Figure 2 illustrates that both particle size and shape were considerably affected by the composition of the feed solution. When pure ethanol was used as the feed solution (Fig. 2B), both shape and size of spray-dried lactose particles were comparable to those of commercial crystalline lactose particles that were not spray dried (Fig. 2A). When the concentration of water in feed material was increased, the number of small and spherical lactose particles increased (Fig. 2C and D). When lactose was spray dried from a pure aqueous feed solution, all particles were very small (<10 μm) and spherical (Fig. 2D).

Table 2 shows that the ratio of ethanol to water affected the crystallinity of the spray-dried lactose. When pure water was used as the feed solution, spray drying produced 100% amorphous lactose. When the ratio of ethanol to water in the feed solution was increased, the degree of disorder in the lactose was decreased in the product. A total, crystalline lactose monohydrate was achieved when lactose was spray dried from pure ethanol.

The solubility of lactose at room temperature is 1 g in 4.63 mL of water, and lactose is practically insoluble in ethanol. When the solubility of lactose in the feed solution was decreased by increasing the ratio of ethanol to water, the amorphous content in the spray-dried lactose decreased (Table 2). This is probably due to the fact that most of the lactose dissolved in the feed solution was solidified as amorphous lactose. The relationship between the fraction of dissolved material in the feed solution and the amorphous content of the spray-dried sample is, however, not straightforward. Chidavaenzi et al.[10] observed that the amorphous content of spray-dried lactose was higher than the dissolved amount of lactose in the feed solution. This might be due to a milling effect on the suspended lactose particles in the atomizer; i.e., milling resulted in the formation of amorphous material by solid-state transition, or enhanced solubility, or more likely a combination of both.[10]

Water content of samples was determined by TG. The surface water of samples removed at 30–90°C, and hydrate water of lactose removed at 80–150°C. Commercial α-lactose monohydrate that was not spray dried contained hydrate water (5.1%)

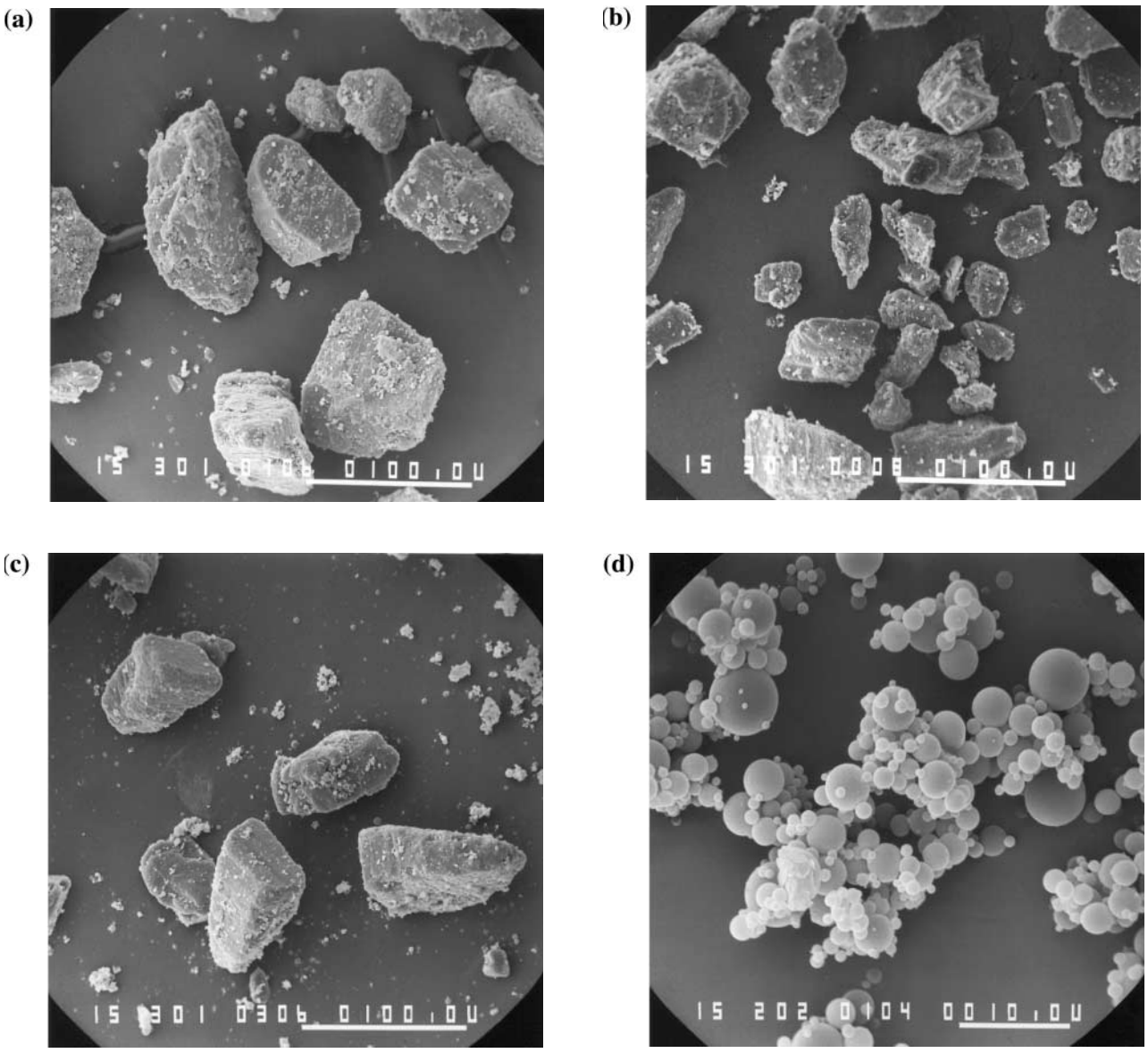

Figure 2. Scanning electron micrographs of untreated lactose (A) and spray-dried lactose samples (B–D). The ratio of ethanol to water in spray drying was 100:0 (B), 40:60 (C), and 0:100 (D). (A–C) Magnification 300×, scale bar 100 μm. (D) Magnification 2000×, scale bar 10 μm.

and no surface water was observed (Table 2). The total amount of water, which included the surface and hydrate water in the spray-dried samples, varied from 3.9% to 5.3% (Table 2). Table 2 shows that the feed solution strongly affected the ratio of surface water to hydrate water, since the content of surface water increased and hydrate water decreased as the crystallinity of the spray-dried lactose decreased. It is well known that the capacity of amorphous lactose for moisture sorption is higher than that of crystalline lactose.[13,14]

Figure 2 illustrates that when the concentration of water in feed material was increased, the number of small and spherical lactose particles increased. Surface area of the spray-dried lactose increased as a function of amorphous content (Table 2) due to the decreased particle size of lactose. The surface area of 100% amorphous lactose was significantly

Table 2

The Ratio of Ethanol to Water in Feed Material and the Consequent Nature of the Spray-Dried Lactose. Concentration of Lactose 15% (w/w). Mean Values (±SD)

Ratio of Ethanol to Water (%) (w/w)	Initial Amorphicity by IMC (%) (w/w) ($n=2$–3)	Amorphicity by DSC[a] (%) (w/w) ($n=1$)	Surface Water (%) (w/w)[a] ($n=3$)	Hydrate Water (%) (w/w)[a] ($n=3$)	α-Lactose Monohydrate (%) (w/w)[a,b]	Surface Area (m^2/g) ($n=5$)
0:100	100	100	3.8 (0.45)[c]	0.1 (0.22)[c]	2	1.61 (0.02)
10:90	80	67	2.9 (0.31)	1.3 (0.23)*	25	2.58 (0.02)*
20:80	76	ND[b]	ND[d]	ND[d]	ND[d]	ND[d]
30:70	36	15	1.5 (0.04)*	3.8 (0.04)*	73	0.75 (0.01)*
40:60	7	6	0.7 (0.15)*	4.6 (0.05)*	88	0.54 (0.02)*
50:50	5	ND[b]	ND[d]	ND[d]	ND[d]	ND[d]
80:20	0.4	0	0.1 (0.03)*	5.2 (0.01)*	100	0.42 (0.01)*
100:0	0	0	0.0 (0.00)*	5.2 (0.00)*	100	0.34 (0.01)*
UTL[e]	0	0	0.0 (0.00)*	5.1 (0.05)*	98	0.29 (0.01)*

[a] Values were determined after storage of samples for several months in a desiccator at room temperature.
[b] Alpha-lactose monohydrate (%) = [hydrate water (%) of sample/5.2%] × 100%.
[c] $n=6$.
[d] Not determined.
[e]Commercial untreated lactose, which was not spray dried.
*The mean difference was significant ($p < 0.05$) compared to 100% amorphous lactose.

smaller than the surface area of 80% amorphous lactose, as the 100% amorphous lactose was fairly cohesive, aggregated to form larger units, and had a reduced surface area.

CONCLUSION

This study shows that the crystallinity of spray-dried lactose can vary from 0% to 100%, depending on the composition of the feed solution. When the concentration of lactose was kept constant in feed suspension, an increase in the ratio of ethanol to water in the feed solution decreased the amorphous content of the spray-dried products. These results indicate that the amorphous content of the spray-dried lactose, as well as the particle size and shape, can be controlled by selecting the appropriate ethanol concentration in the feed solution. The present findings are important, e.g., when highly crystalline drugs and excipients are required for formulations.

ACKNOWLEDGMENTS

This work was financially supported by Focus Inhalation Oy, Leiras Oy, Finnish Cultural Foundation, The Foundation for Advanced Technology of Eastern Finland (P. H.).

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