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Crystallization and X-ray diffraction of spray-dried and freeze-dried amorphous lactose

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Abstract—Crystallization of spray-dried and freeze-dried amorphous lactose over different relative vapor pressures (RVP) and storage times was studied. Crystallization was observed from increasing peak intensities in X-ray diffraction patterns. Lactose was crystallized in samples stored at RVP of 44.1% and above in both types of dehydrated powders. The rate of crystallization increased with increasing RVP and storage time. Similar crystallization behavior of both spray-dried and freeze-dried lactose was observed. Lactose crystallized as α-lactose monohydrate, anhydrous β-lactose, and the anhydrous form of α- and β-lactose in a molar ratio of 5:3 and 4:1 in both spray-dried and freeze-dried forms. Peak intensities of X-ray diffraction patterns for anhydrous β-lactose were decreased, and for α-lactose monohydrate increased with increasing storage RVP and time. The crystallization data were successfully modeled using Avrami equation at RVP of 54.5% and above. The crystallization data obtained is helpful in understanding and predicting storage stability of lactose-containing food and pharmaceutical products.

Keywords: Lactose; Spray drying; Freeze drying; Crystallization; X-ray diffraction

1. Introduction

Amorphous lactose is often produced in freeze-drying and spray-drying processes. Amorphous lactose is metastable and very hygroscopic and therefore sorbs moisture extremely rapidly.[1,2] We believe that the high hygroscopicity of amorphous is the result of the freezing of molecules in a solid solution state leaving hydrogen-bonding sites readily accessible for water molecules.[3] Increasing the amount of sorbed water increases the molecular mobility of lactose, which facilitates the rearrangement of lactose molecules in turn enhancing time-dependent changes such as crystallization.[4,5] Time-dependent crystallization of lactose has been detected at constant relative humidity (RH) from loss of sorbed water during storage,[5–9] and from increasing peak intensities in X-ray diffraction (XRD) patterns.[5,10–12] Crystallization of lactose occurred more rapidly at increasing relative humidities.[7,11,13]

At various relative humidities, lactose may crystallize into different crystal forms, which can be detected by XRD analysis.[5,10,11,14–16] Probable existing crystal types are α-lactose monohydrate, anhydrous β-lactose, and anhydrous forms of α- and β-lactose in molar ratios of 5:3 and 4:1. Prior to dehydration, either by spray drying or freeze drying, mutarotation may occur, which depends on temperature, concentration, and time. Therefore, the degree of mutarotation in spray drying and freeze drying may vary. The types of crystal forms may also depend on material composition, drying method, storage temperature, time, and RH.[10,11,16] Spray-dried lactose crystallized as a mixture of α-lactose monohydrate and anhydrous β-lactose when stored at above 50% RH at 25 °C.[17,18] Würsch et al.[16] observed that only crystalline β-lactose formed in spray-dried milk powder containing 3.14% water at 60 °C after 5 days of storage, but in spray-dried whole milk powders, lactose mainly crystallized as α-lactose monohydrate, when stored at 77% RH at 21 °C.[19]

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It has been reported[5,10,11,17] that freeze-dried amorphous lactose crystallized as a mixture of α-lactose monohydrate and anhydrous β-lactose depending on the RH and temperature during storage. However, in freeze-dried skim milk powder, lactose mainly crystallized as an anhydrous mixture of α- and β-lactose in a molar ratio of 5:3 when stored at 55% RH. When stored at 76.4% and 85.8% RH at 24 °C, stable anhydrous α-lactose and an anhydrous mixture of α- and β-lactose in a molar ratio of 4:1, respectively, were formed.[5]

The rate of lactose crystallization increased with increasing storage RH.[5,11,13,20] In the presence of water, the extent of lactose crystallization may be limited by solubility. Briggner et al.[18] and Sebhatu et al.[21] have reported that the extent of isothermal lactose crystallization was dependent on storage RH in spray-dried lactose. Buckton and Darcy[20] observed that spray-dried lactose crystallized at 50% RH after 11 h and at 75% RH after 47 min of storage. Half-time of lactose crystallization in freeze-dried milk powder was approximately 40, 19, and 8 h at RH of 66.2%, 76.4%, and 85.5%, respectively, but in pure lactose half-times were less at corresponding RH.[5,11] However, the extent of lactose crystallization at isothermal conditions increased slightly, with increasing RH, to a maximum value and then decreased slightly at higher RH conditions at 25 °C.[18,21] So far, there are no comparative lactose crystallization studies between spray-dried and freeze-dried materials. The objectives of the present study were to determine the effects of RVP and storage time on lactose crystallization in spray-dried and freeze-dried lactose at room temperature using XRD, and to determine the rate of lactose crystallization at different RVPs.

2. Experimental

2.1. Sample preparation

An aqueous solution (15% w/w) of α-lactose monohydrate (Dairygold, Mitchlestown, Cork, Ireland) was spray dried using a Niro Atomizer spray drier (Versatile Production Minor Spray-Dryer, Model No. II, Copenhagen, Denmark) as reported by Haque and Roos.[22] Spray-dried powders were collected through two different outlets of the drier as coarse and fine powders. For this study, we used only coarse powders, because, according to our previous gravimetric determinations,[22] there was no time-dependent lactose crystallization differences between coarse and fine powders. The α-lactose solution was also freeze dried using a freeze dryer (Lyovac GT2 freeze-dryer; Amsco Finn-Aqua GmbH, Hürth, Germany) for 60–70 h (temperature < −40 °C; pressure < 0.1 mbar). For freeze drying, the solution was poured into petri dishes (30 mL in each to prepare samples), frozen at −20 °C for 12 h, and subsequently stored at −80 °C for 24 h. The residual water from both spray-dried and freeze-dried samples was removed by keeping samples in vacuum desiccators over P_2O_5 at room temperature (22–23 °C) for at least 5 days. To remove residual moisture, the desiccated spray-dried powders were further dried in a vacuum oven at 50 °C for 24 h before experiments were carried out. Freeze-dried anhydrous samples were ground using a mortar and pestle and powdered samples were stored in evacuated desiccators over P_2O_5 until analyses were carried out.

2.2. Crystallization conditions

Dehydrated spray-dried and freeze-dried samples in vials (≅1.0 g for spray dried and 0.5 g for freeze-dried powder) were stored in vacuum desiccators over different saturated salt solutions at room temperature (22–23 °C). The salts used were K_2CO_3, $Mg(NO_3)_2$, $NaNO_2$, and NaCl (Sigma Chemical Co., St. Louis, Mo, USA) with respective RVP of 44.1%, 54.5%, 65.6%, and 76.1%, giving a water activity (a_w) of 0.01 × percentage of RVP at equilibrium.[23] Samples were removed from the vacuum desiccators at 5, 10, and 24 h, and then every 24 h interval up to 144 h for 65.6% and 76.1% RVP, 192 h for 54.5% RVP, and 480 h for 44.1% RVP. Samples were weighed to obtain sorbed water content after storage. Weighed samples were immediately frozen at −80 °C and freeze dried using the same procedure as when samples were prepared. The dried samples were powdered using a mortar and pestle and stored in evacuated desiccators over P_2O_5 until XRD patterns were measured.

2.3. XRD analysis

The XRD patterns for dehydrated amorphous and crystalline powders were measured by using a Philips X-ray diffractometer (XPERT PRO, PW 3830 generator, PW 3710 MPD diffractometer and PC-MPD software for automatic powder diffraction version 3.0; Philips, Almelo, The Netherlands). The X-ray diffractometer was operated with an anode current of 40 mA and an accelerating voltage of 40 kV. Samples were slightly pressed on an aluminum sample tray using glass slide (75 × 25 mm) and exposed to CuKα radiation at diffraction angles (2θ) from 5° to 30° (step size, 0.02°; time per step, 40.01 s).

The peak search program of the X'Pert HighScore, (Version 1.0a, Philips Analytical B. V., Almelo, The Netherlands) software was used to locate the peaks in XRD patterns by detecting the minima from the second derivative of the diffractogram. Intensity maxima were given as Kα1 net peak height in counts at Kα1 position in degrees.

The types of lactose crystals formed in spray-dried and freeze-dried lactose powder were identified and the

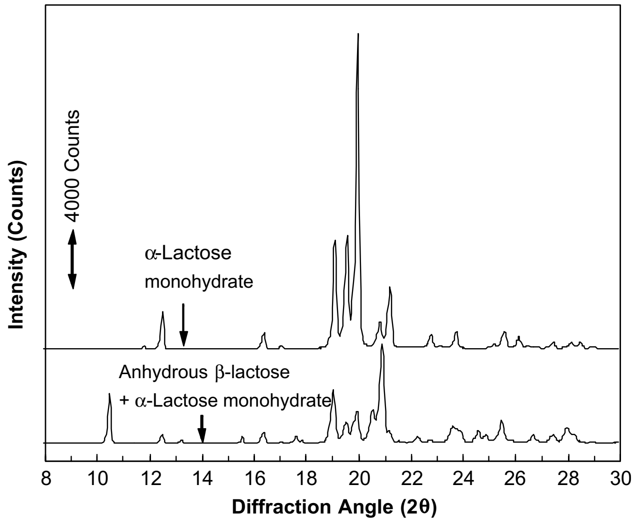

Figure 1. X-ray diffraction patterns for α-lactose monohydrate, and anhydrous β-lactose containing 26% α-lactose monohydrate.

Table 1. Characterization of crystal forms at various diffraction angles (2θ) in XRD patterns

Types of crystals	Diffraction angles (2θ)	References
α-Lactose monohydrate	12.5°, 16.4°	Figure 1, Ref. 14
	20.0°	Figure 1, Refs. 11,24
	20.1°	Ref. 11
Anhydrous β-lactose	10.5°	Figure 1, Ref. 14
	10.5°, 20.9°	Figure 1
	21.0°	Ref. 14
Anhydrous, α:β molar ratio 5:3	19.1°, 20.1°	Ref. 15
	20.0	Ref. 11
Anhydrous, α:β molar ratio 4:1	19.5°	Ref. 15

location of peaks in XRD patterns obtained in the present study were compared with our XRD pattern of pure α-lactose monohydrate (Sigma Chemical Co. Louis, MO, USA) and anhydrous β-lactose (26% α-lactose monohydrate) (Fig. 1) and with reference data shown in Table 1. The progress of lactose crystallization was observed from increasing intensities of peaks in XRD patterns at diffraction angles of 19.1°, 20.0°, and 20.9°.

2.4. Kinetics of lactose crystallization

The Avrami equation[25] (1) was used in the modeling of lactose crystallization data.

$$\theta = 1 - \mathrm{e}^{-kt^n} \tag{1}$$

where θ is crystallinity, t is time, k is a rate constant, and n is the Avrami exponent. The Avrami equation can also be written in the form of Eq. 2.[26]

$$1 - \theta = \frac{I_f - I_t}{I_f - I_0} = \mathrm{e}^{-kt^n} \tag{2}$$

where I_f = a leveling off value of peak intensity occurring at maximum extent of lactose crystallization, I_t = peak intensity at time t, and I_0 = peak intensity of 0 counts for a non-crystalline, amorphous sample. The Avrami equation can also be rewritten in the form of Eq. 3.

$$\ln[-\ln(1 - \theta)] = \ln k + n \ln t \tag{3}$$

Eq. 3 suggests that a plot of $\ln[-\ln(1 - \theta)]$ against $\ln t$ gives a straight line. Linear regression analysis of the experimental data was used to measure the constants, n, corresponding to the slope, and constant, k, from intercept of the line, $\ln k$. Also, the half-time ($t_{1/2}$), the time required to achieve 50% of the maximum extent of crystallinity, was calculated using Eq. 4.

$$t_{1/2} = \sqrt[n]{\frac{-\ln 0.5}{k}} \tag{4}$$

3. Results and discussion

3.1. Crystallization

Spray-dried and freeze-dried amorphous lactose crystallized at RVP ⩾ 44.1%. Time-dependent lactose crystallization was observed from loss of sorbed water.[7,8,22] The XRD technique is another method to confirm the crystallization of lactose from the non-crystalline state of the initial amorphous spray-dried and freeze-dried lactose. Such crystallization was observed in the present XRD patterns. X-ray diffraction patterns for amorphous lactose and lactose stored at RVP of 54.5%, 65.6%, and 76.1% for 144 h are shown in Figure 2. Peak intensities for both types of dehydrated lactose stored at 44.1% were very small, indicating that lactose crystallized slightly at that humidity. The intensities of peaks for spray-dried and freeze-dried lactose increased with increasing storage time until the maximum extent of lactose crystallization occurred at RVP of 54.5% and above.

During the spray drying of lactose solutions temperatures were above 50 °C, which may influence the mutarotation of lactose. As reviewed by Hartel and Shastry,[27] the ratio of α- and β-lactose may change as a result of changes in concentration and temperature in milk. The concentration of lactose solution during spray drying above 50 °C results in saturation of lactose and the formation of small amounts of crystals in amorphous samples. In the present study, this was observed in the XRD pattern of spray-dried lactose, but not observed in freeze-dried lactose (Fig. 2). The initial crystals present in spray-dried lactose may cause slight changes

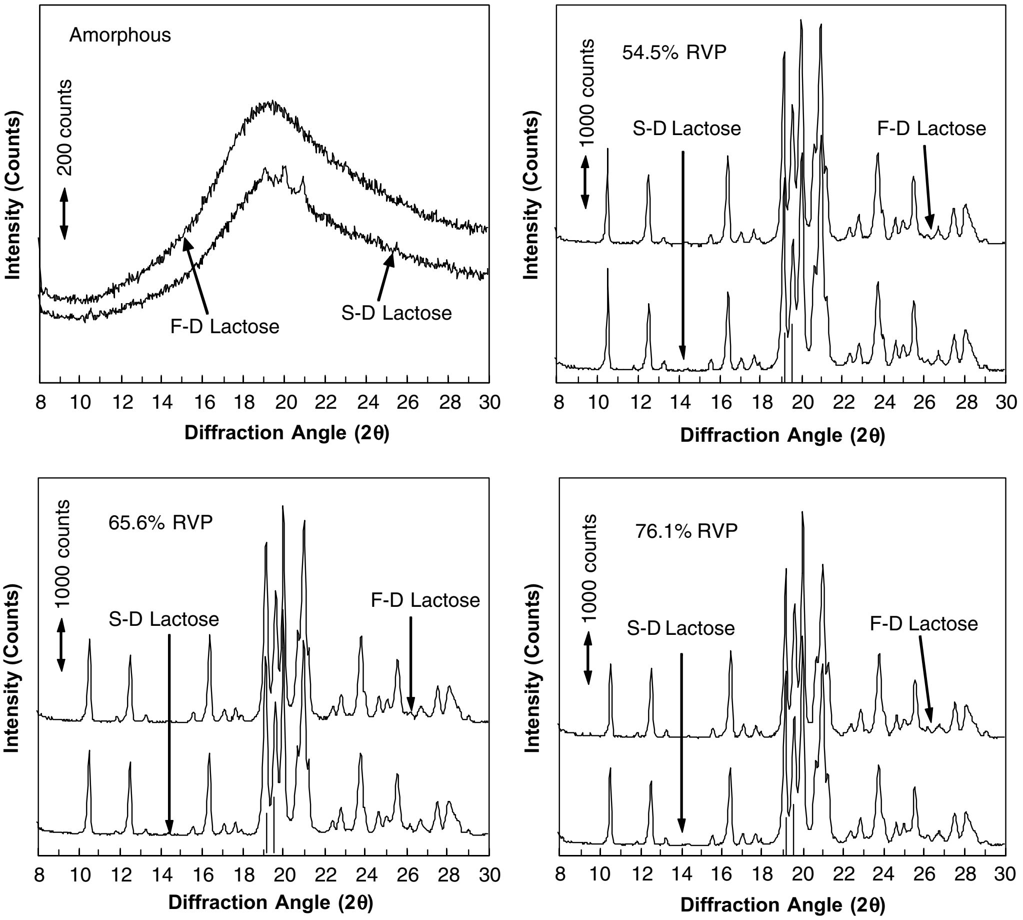

Figure 2. X-ray diffraction patterns for spray-dried (S-D) and freeze-dried (F-D) amorphous lactose and samples stored at relative vapor pressure (RVP) of 54.5%, 65.6%, and 76.1% for 144 h. Peaks for anhydrous mixture of α- and β-lactose in a molar ratio of 5:3 and 4:1 at diffraction angles of 19.1° and 19.5°, used as a reference,[15] are shown by vertical lines.

in water sorption and crystallization behavior of spray-dried lactose as compared with freeze-dried lactose.[3] However, others[5,7,22,28] have shown that the crystallization of spray-dried and freeze-dried lactose occurred during storage at RVP above 37% at 24 °C, which correspond to the critical RVP of lactose. Our XRD patterns in the present study also confirmed the previous studies of lactose crystallization, and similar types of XRD patterns were observed for spray-dried and freeze-dried lactose when stored at RVP $\geqslant$ 54.5% (Fig. 2).

3.2. Types of crystals

Amorphous lactose produced from spray drying and freeze drying stored at 54.5%, 65.6%, and 76.1% RVP crystallized as α-lactose monohydrate, anhydrous β-lactose, and anhydrous forms of crystals with α- and β-lactose in molar ratio of 5:3 and 4:1 (Fig. 2). The types of crystals formed in spray-dried and freeze-dried lactose stored at various RVP were the same. The initial crystals in spray-dried lactose did not influence the type of crystal formed. Bushill et al.,[17] Briggner et al.,[18] and Sebhatu et al.,[21] reported that spray-dried lactose crystallized as mixtures of α-lactose monohydrate and anhydrous β-lactose, when stored at above 50% RH at 25 °C. Jouppila et al.[5] also reported that freeze-dried lactose mainly crystallized as α-lactose monohydrate and anhydrous forms of crystals with α- and β-lactose in molar ratio of 5:3 at RH of 53.8%, 66.2%, and 76.4%; anhydrous β-lactose was formed only in samples stored at 44.4% RH at 24 °C. Freeze-dried lactose crystallized as a mixture of α-lactose monohydrate and anhydrous β-lactose, when stored at 53% RH at 20 °C[10] and at 55% RH at 25 °C.[17] This earlier study reported that, for both spray-dried and freeze-dried lactose, only the anhydrous forms of crystals with α- and β-lactose in molar ratio of 5:3 was observed. Crystals with α- and β-lactose in a molar ratio of 4:1 were not produced. However, in the present study, based upon XRD patterns at diffraction angles of 19.1° and 19.5° (Fig. 2), respectively,[15] crystals with α- and β-lactose in molar ratio but not 4:1 were formed. The variation in crystal types between the present study and other studies might be due to differences in the methods used for production of the α-lactose monohydrate, which was used for the preparation of amorphous lactose, or differences in methods for drying and crystallization conditions.

Peak intensities in XRD patterns for α-lactose monohydrate at a diffraction angle of 12.5° were slightly lower in spray-dried lactose than in freeze-dried lactose. The peak intensities for anhydrous β-lactose, at a diffraction angle of 10.5°, were higher in spray-dried lactose than in freeze-dried lactose samples stored for 144 h at all high RVP. The exception was for α-lactose monohydrate in spray-dried lactose at 65.6% RVP (Fig. 3). In spray-dried lactose, peak intensities for α-lactose monohydrate were slightly higher than in freeze-dried lactose. These results indicated that the amount of α-lactose monohydrate formed was slightly lower and the amount of anhydrous β-lactose slightly higher in spray-dried lactose compared to freeze-dried lactose. However, intensities of peaks for anhydrous β-lactose decreased while those for α-lactose monohydrate increased in both spray-dried and freeze-dried lactose with increasing storage RVP (Fig. 3). For both types of dehydrated lactose maximum intensities of peaks at diffraction angles of 20.0° and 20.9°, which represents the α-lactose monohydrate and anhydrous β-lactose, respectively, was observed. Jouppila et al.[5] also found the maximum peak intensities at diffraction angle of 20.0° in their XRD patterns for freeze-dried lactose. Peak intensities for anhydrous β-lactose decreased and those for α-lactose monohydrate increased in both spray-dried and freeze-dried lactose at RVP of 65.6% and 76.1% with increasing storage time until maximum extent of α-lactose monohydrate formation occurred (Fig. 4). However, peak intensities for anhydrous β-lactose were nearly the same and those for α-lactose monohydrate slightly increased at 54.5% RVP with increasing storage time. These results suggested that unstable anhydrous β-lactose further sorbed water and recrystallized into stable α-lactose monohydrate during storage at RVP of 65.6% and 76.1%. Recrystallization of lactose occurred more rapidly at 76.1% than at 65.6% RVP.

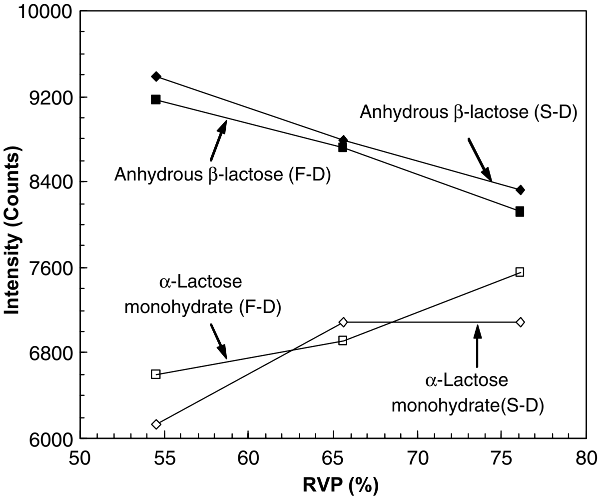

Figure 3. X-ray diffraction intensities as a function of relative vapor pressure (RVP) for anhydrous β-lactose and α-lactose monohydrate at diffraction angles of 10.5° and 12.5°, respectively, in spray-dried (S-D) and freeze-dried (F-D) lactose storage for 144 h.

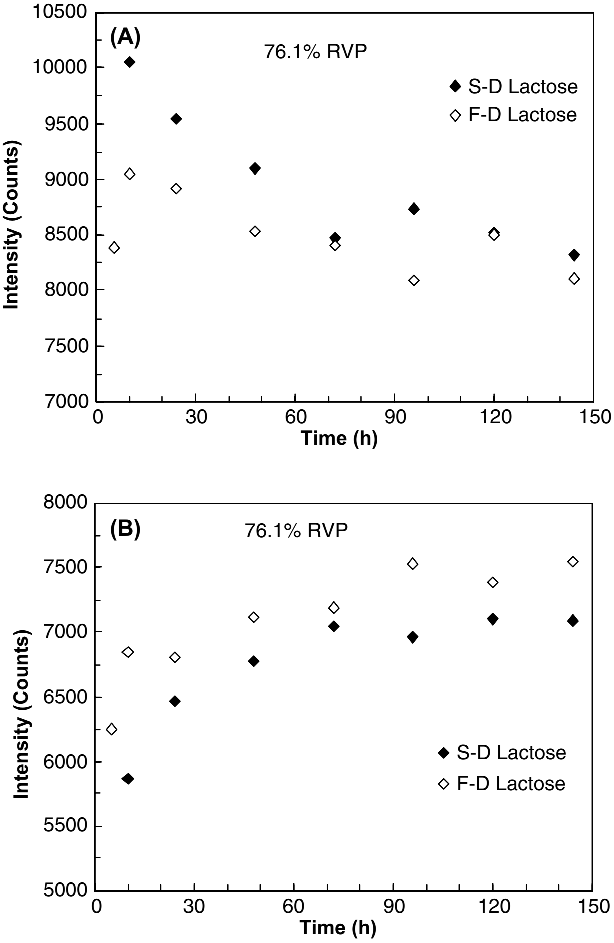

Figure 4. Peak intensities as a function of time in X-ray diffraction patterns at diffraction angle of 10.5° for anhydrous β-lactose (A) and at 12.5° for α-lactose monohydrate (B) in spray-dried (S-D) and freeze-dried (F-D) lactose stored at 76.1% relative vapor pressure (RVP).

3.3. Extent of crystallization

Amorphous lactose crystallized when exposed to conditions favoring crystallization. The crystallization of lactose occurred in a time-dependent manner. The extent of lactose crystallization increased with increasing storage RVP and time. The intensities of peaks in X-ray diffraction patterns for spray-dried and freeze-dried lactose at diffraction angles of 19.1°, 20.0°, and 20.9° leveled off during storage at RVP of 54.5%, 65.6%, and 76.1%, indicating a maximum extent of crystallization (Figs. 5–7). The extent of crystallization and leveling

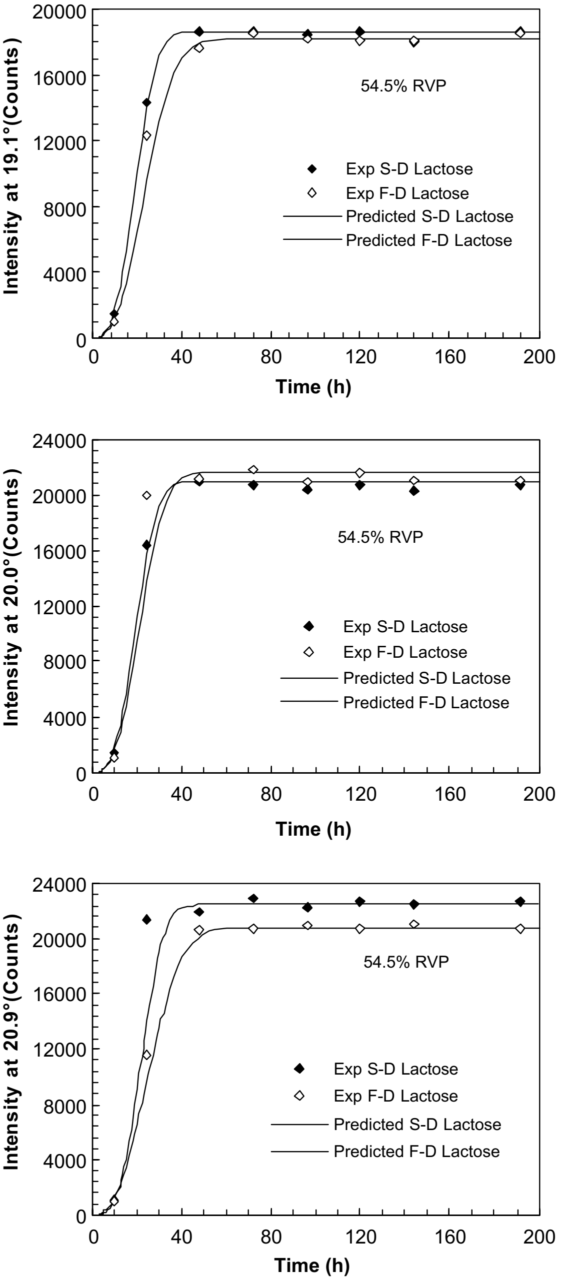

Figure 5. X-ray diffraction intensities at diffraction angles of 19.1°, 20.0°, and 20.9° as a function of time, for spray-dried (S-D) and freeze-dried (F-D) lactose stored at relative vapor pressure (RVP) of 54.5%. The Avrami equation was successfully fitted to the data, as shown by solid and dotted lines for spray-dried (S-D) and freeze-dried (F-D) lactose, respectively.

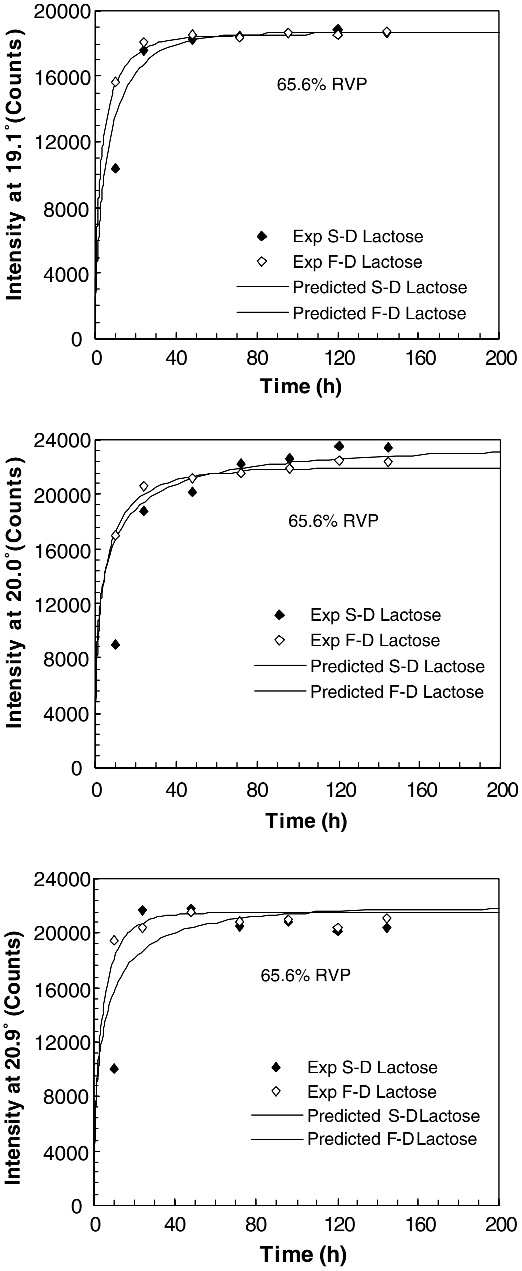

Figure 6. X-ray diffraction intensities at diffraction angles of 19.1°, 20.0°, and 20.9° as a function of time, for spray-dried (S-D) and freeze-dried (F-D) lactose stored at relative vapor pressure (RVP) of 65.6%. The Avrami equation was successfully fitted to the data, as shown by solid and dotted lines for spray-dried (S-D) and freeze-dried (F-D) lactose, respectively.

off values of intensities for spray-dried and freeze-dried lactose differed slightly in samples stored at 54.5%, 65.6%, and 76.1% RVP. The leveling off intensities at a diffraction angle of 20.9° as represented by anhydrous β-lactose for samples stored at 54.5% and 76.1% RVP were slightly higher in spray-dried lactose than in freeze-dried lactose. At a diffraction angle of 20.0° as represented by α-lactose monohydrate and anhydrous form of crystals with α- and β-lactose in a molar ratio of 5:3 intensities were slightly lower in spray-dried lactose than in freeze-dried lactose at RVP of 54.5 (Fig. 5) and 76.1% (Fig. 7). In spray-dried lactose, leveling off intensities at diffraction angle of 20.0° was slightly higher than in freeze-dried lactose at RVP 65.6% (Fig. 6), which was similar as for anhydrous β-lactose at diffraction angle of 10.5° and α-lactose monohydrate at

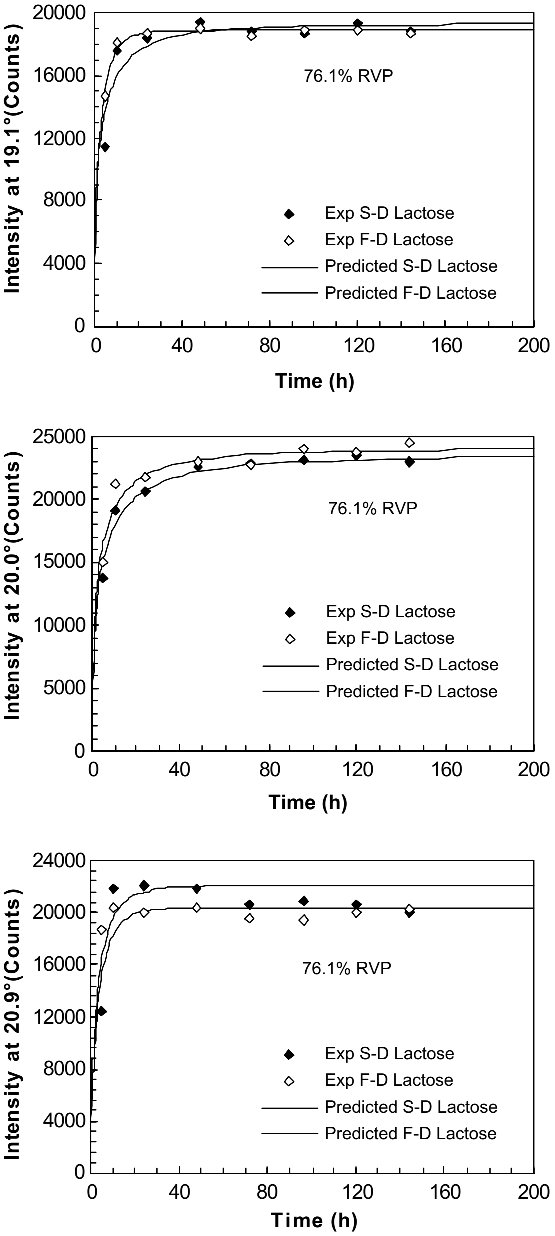

Figure 7. X-ray diffraction intensities at diffraction angles of 19.1°, 20.0°, and 20.9° as a function of time, for spray-dried (S-D) and freeze-dried (F-D) lactose stored at relative vapor pressure (RVP) of 76.1%. The Avrami equation was successfully fitted to the data, as shown by solid and dotted lines for spray-dried (S-D) and freeze-dried (F-D) lactose, respectively.

diffraction of 12.5°. However, the extent of leveling off was reached earlier at higher RVP for both spray-dried and freeze-dried lactose.

The relationship between the extent of lactose crystallization and time could be modeled using the Avrami equation. The Avrami equation was well fitted to the crystallization data obtained at 54.5%, 65.6%, and 76.1% RVP, except the crystallization data at a diffraction angle of 20.9° for 65.6% and 76.1% RVP. The poor fit was probably because anhydrous β-lactose appears at a diffraction angle of 20.9°, and the peak intensities decreased with increasing time after subsequent maximum extent of lactose crystallization. The leveling off values used in the Avrami equation, the values for constant k and n obtained, and calculated half-time are given in Table 2. The Avrami constant, k, increased, and exponent n and half-time of maximum extent of lactose crystallization decreased with increasing storage RVP, as reported by Jouppila et al.[11] and Sperling.[29] For samples stored at RVP 65.6% and 76.1%, the Avrami exponents, n, were nearly the same for both types of materials. Calculated half-times for spray-dried lactose crystallization at 54.5% RVP were slightly lower than for freeze-dried lactose crystallization, and nearly the same at 76.1% RVP for both types of materials. These results indicated that maximum extent of spray-dried lactose crystallization might have occurred earlier than for freeze-dried lactose at 54.5%. Half-times for freeze-dried lactose crystallization at RVP of 53.8%, 66.2%, and 76.4% reported by Jouppila et al.[5] were higher than those obtained for freeze-dried lactose at 54.5%, 65.6%, and 76.1% RVP in the present study, indicating that much more rapid crystallization occurred in the present study. The peak intensities for spray-dried and freeze-dried lactose against time at diffraction angles of 19.1°, 20.0°, and 20.9° showed a sigmoid relationship (Fig. 5) at RVP of 54.5%, as was observed by Jouppila et al.[11] in freeze-dried skim milk powder at diffraction angles of 19°, 20°, and 22° at RH of 66.2%, 76.4%, and 85.8%, but not at 65.6% and 76.1% RVP. Jouppila et al.[5] also did not observe sigmoid relationships of peak intensities against time in freeze-dried lactose at RVP of 66.2% and 76.4%. A probable reason is that pure lactose crystallized very rapidly at RVP of 65.6% and above. However, the types of crystals formed and the maximum crystallization extent at higher RVP were independent of the drying method and only slightly different rates of lactose crystallization between spray-dried and freeze-dried materials were observed.

4. Conclusions

Amorphous spray-dried and freeze-dried lactose crystallized as α-lactose monohydrate, anhydrous β-lactose, and anhydrous forms of crystals with α- and β-lactose in a molar ratio of 5:3 and 4:1 at RVP ⩾ 54.5%. The extent of lactose crystallization was dependent on storage RVP. In both spray-dried and freeze-dried lactose, the intensity of peaks in the XRD patterns for anhydrous β-lactose decreased while those for α-lactose monohydrate increased with increasing storage RVP and time. Recrystallization of unstable β-lactose into stable α-lactose monohydrate occurred during storage at RVP of 65.6% and 76.1%. The rate of lactose crystallization in-

Table 2. Leveling off values for the maximum extent of spray-dried and freeze-dried lactose crystallization stored at various relative pressures (RVP), values of the constants in the Avrami equation, and half-time of lactose crystallization (time required to achieve 50% of the maximum extent of crystallinity), calculated using the constants k and n

Storage RVP (%)	Peak intensity (I) indicating the extent of lactose crystallization[a]	Leveling off value (counts)[b]	Values of the constants in the Avrami equation		R^2 $(n)^{\mathrm{c}}$	Half-time (h)
			k (h^{-1})	n		
Spray-dried						
54.5	I at 19.1°	18,642	1.3×10^{-4}	2.9	0.99(3)	19.3
	I at 20.0°	21,013	1.1×10^{-4}	2.9	0.98(3)	19.4
	I at 20.9°	22,425	3.2×10^{-5}	3.2	0.93(4)	22.0
65.6	I at 19.1°	18,689	2.7×10^{-1}	6.7×10^{-1}	0.88(5)	4.1
	I at 20.0°	23,438	4.9×10^{-1}	4.0×10^{-1}	0.94(5)	2.4
	I at 20.9°	21,837	4.1×10^{-1}	4.9×10^{-1}	0.79(5)	2.9
76.1	I at 19.1°	19,270	6.0×10^{-1}	4.6×10^{-1}	0.75(4)	1.4
	I at 20.0°	23,457	5.1×10^{-1}	4.5×10^{-1}	0.94(4)	2.0
	I at 20.9°	22,040	4.8×10^{-1}	6.6×10^{-1}	0.67(3)	1.7
Freeze-dried						
54.5	I at 19.1°	18,144	1.5×10^{-4}	2.6	0.96(3)	23.7
	I at 20.0°	21,603	1.3×10^{-4}	2.8	0.87(4)	21.4
	I at 20.9°	20,733	1.8×10^{-4}	2.6	0.97(4)	25.4
65.6	I at 19.1°	18,606	4.4×10^{-1}	6.0×10^{-1}	0.92(5)	2.2
	I at 20.0°	21,943	4.4×10^{-1}	5.3×10^{-1}	0.98(5)	2.3
	I at 20.9°	21,544	3.9×10^{-1}	6.7×10^{-1}	0.86(4)	2.3
76.1	I at 19.1°	18,846	5.2×10^{-1}	7.2×10^{-1}	0.95(4)	1.5
	I at 20.0°	24,003	5.6×10^{-1}	4.6×10^{-1}	0.83(4)	1.6
	I at 20.9°	20,403	4.5×10^{-1}	7.0×10^{-1}	0.67(3)	1.8

R^2 for the linear regression, and $(n)^{\mathrm{c}}$ the number of points used in the regression analysis.

[a] Peak intensities at diffraction angles of 19.1°, 20.0°, and 20.9° are indicated with I and respective diffraction angle.

[b] The number of observations used in calculation with corresponding storage time is 6 (48–192 h), 5 (48–144 h), and 6 (24–144 h) at RVP of 54.5%, 65.6%, and 76.1%, respectively.

creased as RVP increased. The crystallization data obtained in the present study were successfully modeled using Avrami equation, which may be helpful for understanding and predicting the storage stability of lactose-containing food and pharmaceutical materials.

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