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Thermal and X-ray Diffraction Analysis of Lactose Polymorph

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Abstract

Different preparation methods and techniques were utilized to explore the crystallization behavior of the anhydrous lactose crystals prepared from α-lactose monohydrate. The crystal morphology of the obtained polymorphs was observed by SEM and the structural characterization of the samples was carried out by XRD. And several typical crystal shapes have obtained in the experiment, such as tomahawks, diamond-shaped plates and pyramids. The anhydrous α-lactose form obtained by rapid dehydration exhibits the same X-ray peaks as the monohydrate. The presence of lactose polymorphs in the test samples was determined by DSC and the weight loss was measured by TGA. This study supplied some methods to prepare the anhydrous lactose and discovered a dehydration peak of β-lactose in the TGA picture at approximately 125 °C.

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Keywords: α-lactose monohydrate; crystallization; anhydrous lactose; thermal analysis; polymorphs

1. Introduction

Lactose, which is composed of D-glucose and D-galactose, is a kind of disaccharide [1]. A distinctive feature of lactose is the manifestation in different crystal structures and temperature-dependent physico-chemical interrelationships. The production of powders with controlled and desired product properties has always been a challenge, especially in pharmaceutical [2] and food industry [3]. Most of the academic and industrial research groups now recognized the importance of detecting polymorphic forms and solvated varieties at the earliest stage of development of potential new drugs.

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α-Lactose monohydrate (Lα•H_2O) is the most common form, which is relatively nonhygroscopic. Its physico-chemical properties, crystallization and dehydration behaviors have also been studied [5-7]. The types of crystal forms may depend on material composition [8, 9], drying method, storage temperature, time, and relative humidity [10, 11], etc. Three out of four lactose polymorphs: Lα•H_2O, unstable hygroscopic anhydrous α-lactose (LαH), and β-lactose (Lβ, less hygroscopic), crystallize with monoclinic unit cells [4]. The crystal structure of the stable anhydrous α-lactose (LαS) is a more complex triclinic unit cell.

Lactose with different characteristics can be prepared by different methods. For example, adding alcohol in lactose solution can decrease the solubility of lactose [12]. Anhydrous forms of α-lactose can be produced either in vacuum or in air under different temperature [8]. The preparation temperature of LαS is higher than LαH [13]. There are several methods to prepare LαS [14, 15] and LαH [13, 15, 16]. It has been reported by Figura and Epple [14] that LαH is a precursor of LαS. LαS can be prepared from Lα•H_2O at 160-170 °C, which has been demonstrated by DSC and XRD [4]. There are several methods developed for the preparation of the other important anhydrous forms. For instance, Lβ can be prepared by adding some different effective solvents, such as methanol, ethanol and n-butanol [13, 17, 18].

Different crystal forms of lactose crystals are of great interest to industrial crystallization, especially in the area of food, pharmaceutical and fine chemicals, as the physicochemical properties of solubility, density, stability, and bioavailability depend directly on the polymorphs. However, few studies have been investigated the effects of crystallization conditions on the crystal habit of lactose, such as particle size and particle shape. The crystal habit of Lα•H_2O varies greatly under different condition of crystallization [19-22].

In order to explore some methods to prepare the dehydrated forms of lactose by Lα•H_2O, this paper mainly discusses the lactose crystallization in aqueous solution, methanol, ethanol and acetone. Some of the anhydrous samples were generated by the direct-dried method. The obtained polymorphs were characterized by SEM to investigate morphologic features. The structures of the polymorphs were investigated by XRD. The obtained crystals were characterized by DSC and TGA to assess the dehydration onset temperature and the weight loss.

2. Experimental

2.1. Materials

Lα•H_2O (Respitose SV001 from DMV International, Veghel, The Netherlands) was chosen as the model material for it is well-known as an amorphous form. The raw material was employed with no further purification. All other chemicals were analytical grade. In all experiments, distilled water was used.

2.2. Sample preparation

Preparation of LαS: LαS was prepared by two similar methods. The first method: The samples were prepared at room temperature, and methanol and ethanol were dried before used. A certain amount of Lα•H_2O were added into methanol and ethanol, respectively. All these samples were put into shaking table directly, shaken for 48 h and dried at 90 °C. The second method: The equal mass of Lα•H_2O was added into methanol ($H_2O \leqslant 0.01\%$) under stirring at room temperature, and the solution was heated at 90 °C.

Preparation of LαH: the direct-dried sample (Fig. 1) was prepared by heating Lα•H_2O in a non-covered petridish at 105 °C for at least 4 h [23]. Except the direct-dried method above, there were two different methods to prepare the LαH. The first method: LαH was formed by using dewatered acetone as the solvent. The second was thermal dehydration method: Lα•H_2O aqueous solution was heated at 110 °C. The LαH samples were dried for storage before the further analysis.

Preparation of β-lactose: Lα•H_2O was added in methanol aqueous solution at ambient temperature, and then was heated slightly to 95 °C.

2.3. Analytical techniques

SEM images were obtained using an Ultra 55 field emission SEM (Carl Zeiss NTS GmbH, Oberkochen, Germany).

X-ray diffraction (XRD) was carried out on a D8 Advance (Bruker AXS, Germany). The XRD patterns were recorded in the range of 2θ from 20° to 70°.

Differential Scanning Calorimetry (DSC) measurements (DSC 2920, TA Instruments, USA) were carried out at a heating rate of 10 K min-1 up to different temperature with 3～10 mg of sample in reference pan. In order to avoid any reactions with air, Helium (He) was used as a purge gas with a flow rate of 25 mL min-1. DSC involves the heating or cooling of a sample and reference and the measurement of the differential heat flow between them with respect to temperature.

Thermogravimetric measurements were carried out on a Q50 Thermoanalyser (TA Instruments, USA), at a heating rate of 10 K min^{-1} with nitrogen as a carrier gas.

3. Results and Discussions

3.1. Crystal morphology of the dehydration samples

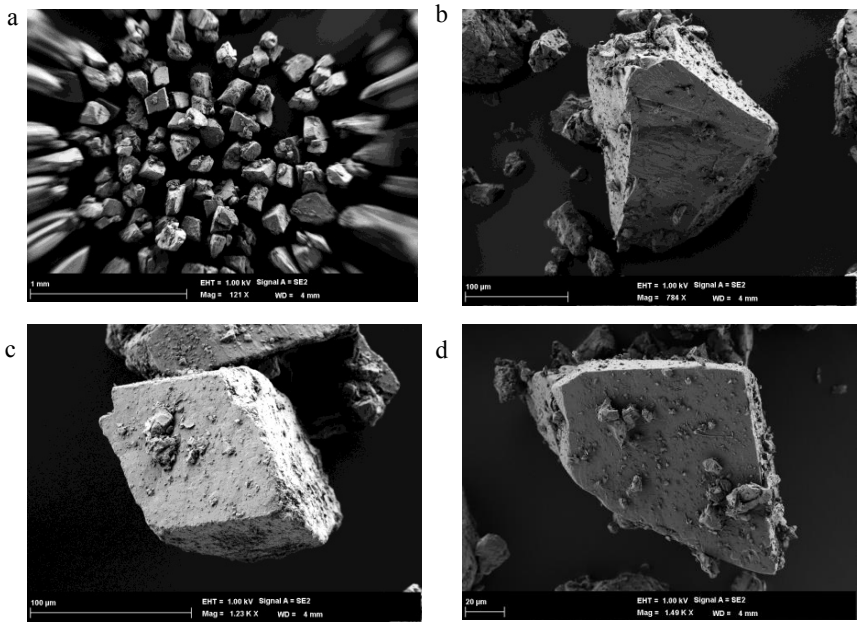

Fig.1. (a) SEM pictures of α-lactose monohydrate samples; (b), (c) and (d) the partial enlarged drawing of (a).

The LαH crystal morphology of the direct-dried samples was showed in Fig.1. It can be seen that there were several typical crystal shapes, such as tomahawks (Figure b), diamond-shaped plates (Figure c) and pyramids (Figure d). From the Figure a, agglomeration can be avoided by the drying process. Besides, the dehydrated form can be prepared by heating Lα•H_2O crystals in an appropriate temperature which is high enough to drive off the water [14].The dehydrated sample obtained at 105 °C was inferred to an anhydrous α-lactose, and this inference was confirmed by the following detection results (Fig.5).

Tomahawk is a familiar shape of lactose. These samples were obtained from the evaporation of Lα•H_2O aqueous solution. There are two anomers in lactose aqueous solution, α-lactose and β-lactose, and they can keep balance by mutarotation according to a certain proportion [3]. As α-lactose hydrate is less soluble than the β form, it precipitates

from this solution in the evaporation process. During this crystallization process, β-lactose acts as both a nucleation inhibitor and a habit modifier [24]. Then the concentration of α-lactose in the solution will decrease, and β form will turn into α-lactose until the system reaches a new equilibrium which exists of 40α:60β between anhydrous α- and β-lactose [4]. Meanwhile, the crystal habit is related to the super saturation, and the growth rate could be various at different faces when the concentration is decreased [25], then the dominant crystal form pyramids (Fig.1. (d)) changed to tomahawks (Fig.1. (b)). Based on the present of Fig.1. the crystal form of tomahawks had a highly asymmetric. It can be concluded that the crystal shapes of the LαH samples prepared by different methods were similar.

3.2. X-ray diffraction (XRD)

The XRD patterns of lactose crystallization samples were observed in Fig.3. Patterns A, C and D were detected by samples that formed in aqueous solution, methanol aqueous solution and ethanol aqueous solution, respectively. Pattern B represented for raw material. Compared with the patterns of sample B, the structure of the sample A is different. From the A and C, the similar peaks indicate that they have the same crystal structure. According to the earlier work [13], it can be speculated that both A and C were LαS.

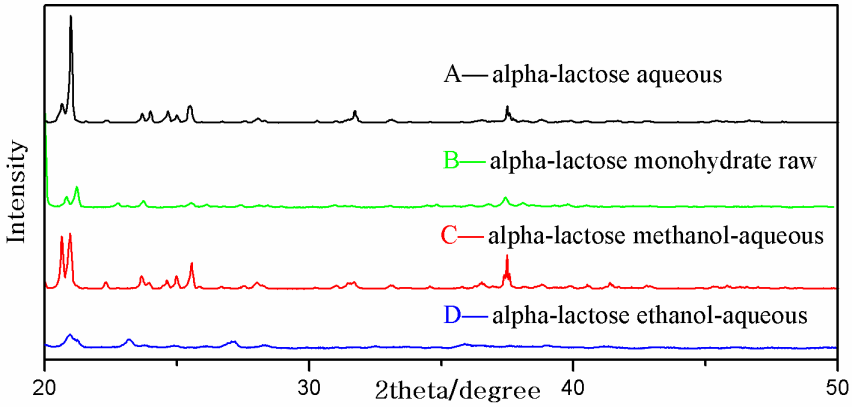

Fig.2. the X-ray patterns of Lα•H_2O subjected to different methods of dehydration.

The anhydrous α-lactose formed by alcohol treatments are all distinct species [8] which was clearly proved in Fig.3. The patterns of C and D were obtained from Lα•H_2O treated by methanol and ethanol respectively. Both methanol and ethanol can make the solubility of lactose decrease [15] and accelerate the crystallization process. Furthermore, according to the XRD curves, LαS would be produced when Lα•H_2O was treated with ethanol.

3.3. Thermal analysis

The lactose samples had different characteristic peaks, as shown in Fig.4. The endothermic peak at 145°C is the dehydration peak of Lα•H_2O [26]. According to the endothermic peak showed at approximately 235°C and the previous work of Figura & Epple [13], it can be concluded that the sample was Lβ. Therefore, it can be deduced that Lβ could be formed not only in acetone [15], but in methanol aqueous solution .

The LαH samples which was obtained from dewatered acetone showed that there was one exothermic peak at about 145 °C. This temperature has been interpreted as the transformation temperature of Lα•H_2O [13]. According to the TGA curve and the research of Garnier et al. [15], it was found that the peaks of the dehydrated sample at 105°C (showed in Fig.5) were also consistent with the monohydrate. It can be concluded that this sample was LαH.

As seen in Fig.4, the LαS samples which were formed by different preparation methods showed one endothermic peak at 210-220 °C. The multiple peaks above 200 °C were related to the melting point of the samples [27, 28]. Only LαS forms were left when the temperature exceeded 200 °C. From the DSC curves, it can be concluded that

not all of the samples exhibited the characteristic dehydration peak of Lα•H_2O. Furthermore, Gombás et al. [28] considered that with the increase of the crystalline fraction, the height of the exothermic peak (typical for amorphous form) and its energy value decreased. This theory was a good interpretation to explain the height of the exothermic peak.

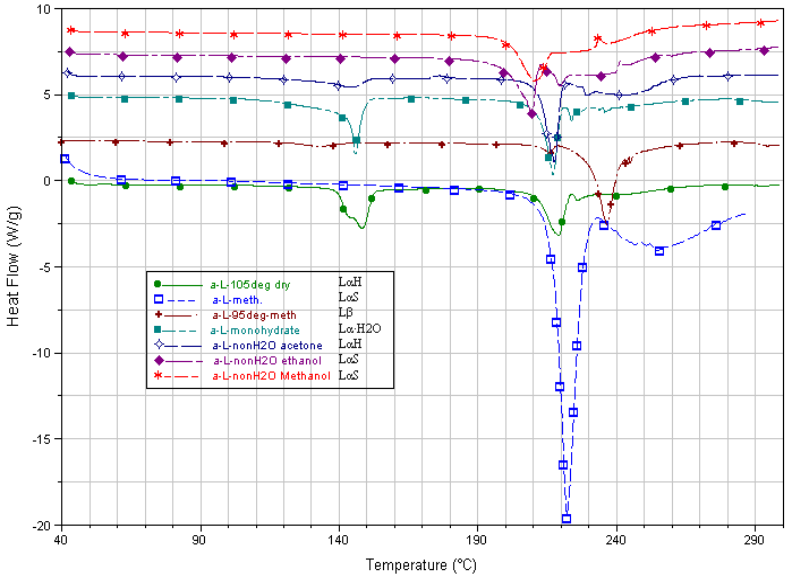

Fig.3. DSC curves of Lα•H_2O subjected to different conditions of dehydration.

The dehydrated onset temperatures of the as-prepared samples were shown in TGA curves. According to the number of the constant weight curves, the difference between Lα•H_2O and other samples had been shown. It can be concluded that Lα•H_2O undergoes two mass decreases. The first mass decrease was predicated to the loss of water, and the corresponding temperature of the mass decrease was lower than the boiling point of water.

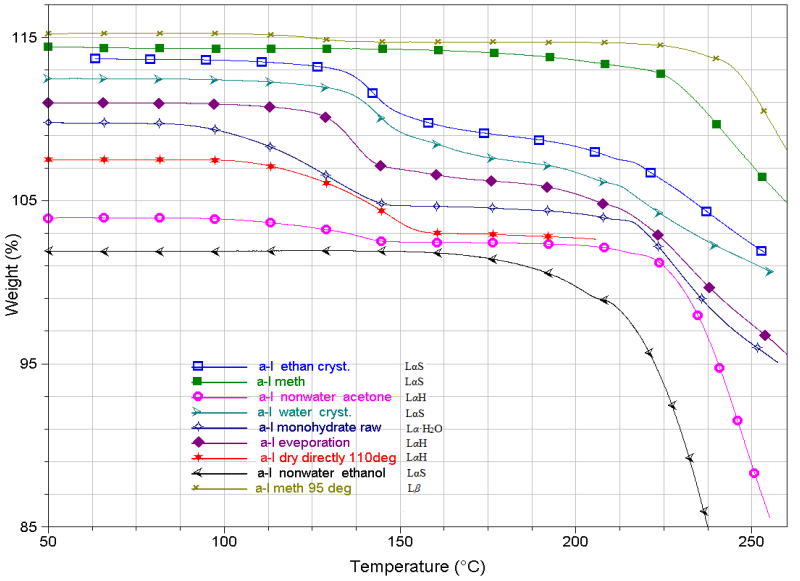

Fig.4. TGA curves of Lα•H_2O subjected to different conditions of dehydration.

Nevertheless, the LαH samples which were claimed to have the same peaks with Lα•H_2O in Fig. 4 showed a higher water loss temperature than Lα•H_2O, even higher than the water boiling point. In order to explain this phenomenon, Crisp et al. [29] suppose that the boiling point increased effectively to overcome any forces of attraction which caused by the interactions within the lattice. Comparing to the peak position of water loss, it can be concluded that the interactions in lattice increased the boiling point. The second mass decrease peaks indicated the decomposition of the samples (onset at approximately 220 °C).

In accordance with the above experimental results, it can be found that the TGA fully complied with the DSC analysis result. While to the Lβ sample, it can be hardly found that there was a peak at about 130 °C in DSC, but a small weight loss found in Fig.5 at approximately 125 °C, and it could be confirmed that Lβ is hygroscopic. Furthermore, Lβ has a higher decomposition temperature than others. The unique mass decrease was associated with the direct decomposition of the samples.

4. Conclusion

The dehydration mechanism of molecular hydrates is displayed in this study, using a combination of complementary techniques associated with structural data. Several typical crystal shapes have obtained in the experiment, such as tomahawks, Diamond-shaped plates and Pyramids. The LαS produced by dehydration of Lα•H_2O had the same structure as anhydrous lactose prepared by crystallization from dry methanol and ethanol. The LαH form obtained by rapid dehydration of Lα•H_2O exhibits the same X-ray peaks as the monohydrate. When dehydration is induced by heating, the reorganization of the anhydrous material is varied due to the formation of the hygroscopic LαH. Further heating is required to induce the polymorphic transformation towards the stable anhydrous LαS form. The Lβ form cannot only be produced in dry acetone, but can be formed in methanol aqueous solution in mild conditions without stirring. TGA and DSC data showed that changes of the dehydration behavior of samples depended on different dehydration process. The thermal properties and crystallization behavior obtained in the present study may be helpful for the understanding and predicting the storage stability of lactose-containing food and pharmaceutical materials.

Acknowledgements

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