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Anti-Solvent Crystallization of Lactose Single Crystals from Alcohol-Aqueous Solution at different concentrations

P. Parimaladevi and K. Srinivasan*

Crystal Growth Laboratory, Department of Physics, School of Physical Sciences, Bharathiar University, Coimbatore - 641046, Tamil Nadu, India.

***Corres.author: nivas_5@yahoo.com**

Abstract: Anti-solvent crystallization of lactose from aqueous solutions with different concentrations of ethanol was studied at constant temperature. Supersaturation generated within the system and the induction times of nucleation were measured and the variations in morphology of the nucleated crystals were analyzed with different anti-solvent concentrations. At lower concentration of ethanol, larger crystals were nucleated with longer induction time and the crystals had tomahawk morphology. At higher concentration, small crystals were nucleated with shorter induction time and the crystals had needle-like morphology. Powder x-ray diffraction (PXRD) and differential scanning calorimetry (DSC) analyses revealed that the variation in morphology of the grown crystals mainly depends on the change in composition of the different pseudo-polymorphic forms of lactose formed at different experimental conditions. By employing anti-solvent crystallization process we could able to crystallize α-LM crystals within a short period of time and with narrow crystal size distribution (CSD).
Key words – lactose; anti-solvent; nucleation; growth from solutions; morphology.

Introduction and Experimental

Lactose (β-D-galactopyranosyl(1-4)-D-glucopyranose), the main sugar of milk exists in two isomeric forms alpha-lactose (α-L) or β-lactose (β-L) depending on the α-or-β-glucose isomerization in aqueous solution and in association with water molecules in the solid state [1, 2]. α-L also exists in three pseudo-polymorphic forms, alpha-lactose monohydrate (α-LM), stable alpha-lactose anhydrous (α-L_S) and unstable alpha-lactose anhydrous (α-L_H). Excellent flowability, compactability and stability of α-LM make it as a more suitable candidate for dry powder inhalers (DPIs) than any other forms [3]. Due to the interconversion of lactose molecules in aqueous solution, α-LM crystals nucleated only after a long period of time with slower growth rate and with wider CSD [4]. To reduce the nucleation time and CSD and to enhance the growth rate anti-solvent crystallization technique was employed.

Saturated aqueous solution of α-LM was prepared at 34 °C and the solution was filtered with Whatmann no. 2 filter sheets followed by vacuum filtration. The filtrate was taken in nine similar test tubes (80 ml capacity) with different volumes from 3 to 27 ml in steps of 3 ml and 1.5 ml of the filtrate was taken in another one. Ethanol (polar protic solvent), an anti-solvent was added to the above solutions with different

concentrations such that the anti-solvent occupied 10-90 % (in steps of 10%) and 95 % v/v of the total crystallization volume. pH value of the pure α-LM aqueous solution, pure ethanol and each of the experimental solution after the addition of ethanol was measured using EUTECH pH tutor instrument. Test tubes were tightly covered and the experimental solutions were kept inside the constant temperature bath maintained at 34 °C. The solutions were carefully monitored for the occurrence of nucleation event and left undisturbed for 48 h to the growth of nucleated crystals. Supersaturation generated within the solution and induction time were measured. Morphology of the nucleated crystals was examined at different time intervals under the optical microscope. Grown crystals were carefully harvested and subjected to PXRD and DSC analysis.

Results and Discussion

Addition of different volumes of ethanol greatly reduces the solubility of α-LM in solution and it leads to the generation of higher supersaturation within the system as shown in Fig.1a. While adding 10-20% v/v ethanol, there is no nucleation observed up to 48 h because the supersaturation (i.e. σ=0.02-0.18) generated within the system is inadequate to induce the nucleation. Solutions contain 30-90 and 95% v/v ethanol nucleate at 1200-0.66 and 0.25 min, respectively because the supersaturation generated within the system is greatly increased from σ=0.19 to σ=5.27. Induction time of α-LM nucleation was significantly decreased with increase in ethanol concentration. pH value of the experimental solution is also increased with increase in ethanol concentration and the variation in pH of the solution at the time of nucleation (i.e. initial pH) and crystal harvesting (i.e. final pH) is shown in Fig. 1b. When ethanol concentration is increased, the nature of the solution turned from more acidic to neutral and the probability of existence of α and β-L is slightly changed. The initial and final pH values exhibit similar pattern, show only slight variations until the end of the experiment.

While increasing the concentration of ethanol from 30 to 60% v/v, α-LM crystals nucleated with tomahawk morphology and the size of the nucleated crystals also increased with ethanol concentration as shown in Fig. 2 a and b. When ethanol concentration is in the range 70-95% v/v, α-LM crystals nucleated with needle-like morphology and size of the nucleated crystal getting reduced with ethanol concentration. Nucleated crystals are stable within the solution itself and the crystals are gradually losing their stability when they exposed to atmosphere along with the experimental solution. The tendency of absorption of water molecules from the surrounding gets increased with increase in ethanol concentration and hence the solubility of α-LM crystals increased leading to the dissolution of nucleated crystals. Once the crystal is separated from the solution and dried it become stable at normal conditions.

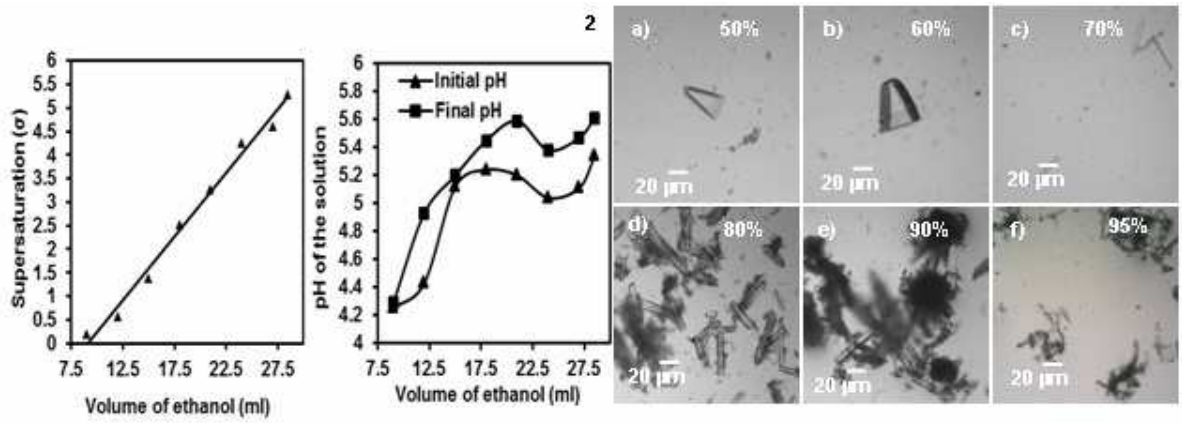

Fig 1. a) Variation in supersaturation and **b)** variation in pH as a function of ethanol concentration.

Fig 2. Snapshots of nucleated crystals in the ethanol concentration range 50-95% v/v.

The rate of nucleation and the tendency of nucleation of other pseudo-polymorphic forms also get increased with increase in ethanol concentration. At lower anti-solvent concentrations (i.e. from 10 to 60% v/v), nucleation of α-LM crystals become dominant. Whereas at slightly higher anti-solvent concentration (i.e. 70% v/v), nucleation of α-LM get reduced and the nucleation of other polymorphs become dominant. PXRD and DSC analysis of the grown crystals shown in Fig. 3 (a and b, respectively). The characteristic PXRD peak for α-LM was observed at 20º 2θ and it became more prominent only at lower anti-solvent concentrations. The

characteristic PXRD peak for β-L was observed at 10.55º 2θ which became more prominent at higher anti-solvent concentrations. DSC results also show similar results that α-LM crystals dominantly nucleate at lower anti-solvent concentration and β-L at higher anti-solvent concentrations. The endothermic peak observed at 140-150 ºC indicates the removal of water of crystallization form α-LM crystals whereas the peak observed at 200-215 ºC shows the melting of α-LM crystals. The peak observed at 220-230 ºC indicates the melting of β-L crystals.

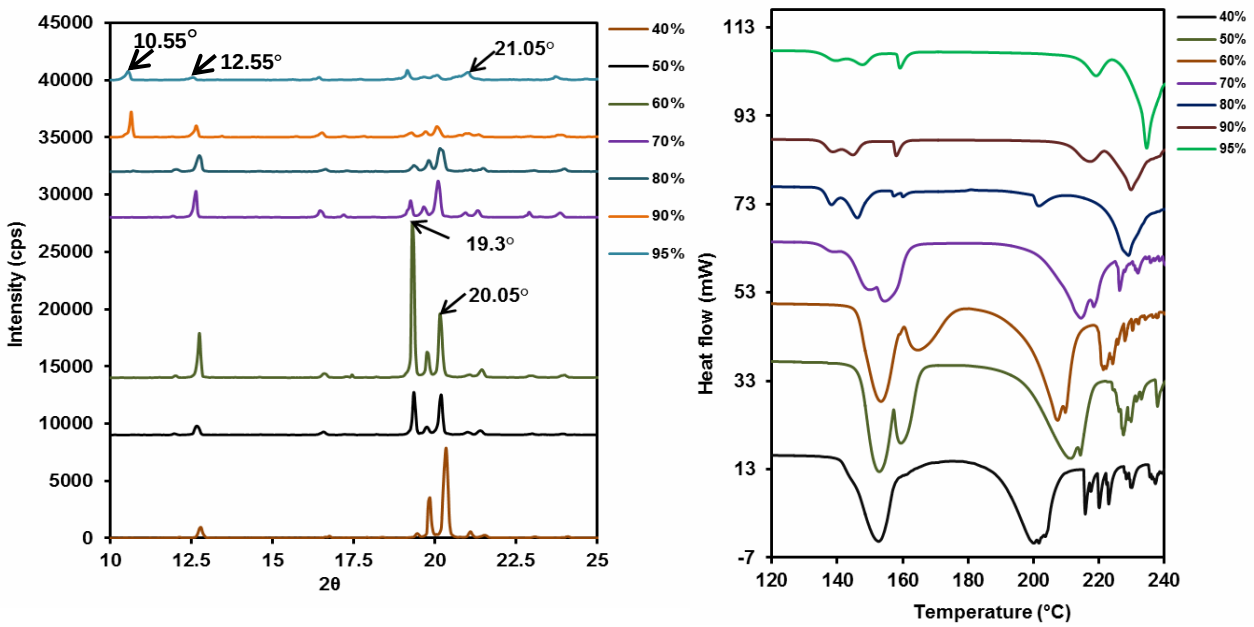

Fig. 3 a) PXRD pattern and b) DSC analysis of grown lactose crystals in the ethanol concentration range 40-95%.

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