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Analysis of stochastic crystallization in micron-sized droplets of undercooled liquid L-arabitol

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ABSTRACT

Kinetics of isothermal crystallization of L-arabitol were analyzed from the undercooled liquid state within micron-sized droplets from micro-Raman spectroscopy. This study reveals that crystallization slightly above T_g is controlled by stochastic heterogeneous nucleation inherent to the droplet size. Microscopic Raman investigations performed in droplets give the unique opportunity to analyze the pure metastable Form II of L-arabitol. It was found that Form II is characterized by a molecular packing more compact than that of the stable Form I, inherent to strong intermolecular hydrogen bonding. Kinetics laws obtained by analyzing several droplets at different temperatures, reveal the transient character of Form II, quasi systematically detected during the crystallization process of form I. Form II appears as the first step of crystallization prior to successive short-living metastable states which is necessary to achieve a complete crystallization in Form I. It was found that the kinetics of conversion between the metastable states (Form II) into Form I is dependent on the amount of strong hydrogen bonding distinctive of Form II.

1. Introduction

Arabitol, $C_5H_{12}O_5$, belongs to the family of pentitols and more generally to the polyol family. It is characterized by the existence of two enantiomorphs, D- and L-arabitol. The L form can be prepared by the catalytic reduction of arabinose, while D-arabinitol is naturally found in lichens and mushrooms. Polyols are high value products in the area of pharmaceutical and agrochemical industries, since they are commonly used as excipients in formulations for tableting, spray-drying and freeze-drying [1] procedures. In this context, information on the physical properties, including phase transformation temperatures, polymorphism, physical stability, should be relevant in the application of these materials to the manufacturing processes. The analysis of crystalline conversion of amorphous states, and the complex polymorphic transitions of these materials [2] are required to avoid unexpected crystallization. Two polymorphic forms of L-arabitol have been revealed. Form I is the commercial phase, characterized by the triclinic P1 space group [3] and stabilized by the O–H···O hydrogen bond network [3]. Form I melts upon heating at $T_{m,I} = 101$ °C [4,5]. The existence of the metastable Form II was detected from differential scanning calorimetry [6,7] and X-ray diffraction [7] investigations, and characterized by a lower melting temperature $T_{m,I} = 83$ °C [6,7]. However, the thermal conditions of preparing Form II remain unclear. Moreover, X-ray diffraction patterns isothermally collected at 0 °C have revealed that Bragg peaks of form II emerging from the halo of the undercooled liquid, disappear at the expense of those of the growing Form I [7,8]. No diffraction pattern of pure Form II was obtained.

Micro Raman spectroscopy gives the opportunity to analyze the crystallization from the liquid state in droplets at the micrometer scale, and provides structural information about polymorphic forms. In order to obtain a better insight into the metastable phase formation process and more generally into the mechanism of crystallization from the undercooled liquid state, micro Raman spectroscopy investigations were carried out during isothermal transformations at T = 265 and 273 K. Raman spectra of polymorphic forms were collected in a wide spectral range to analyze structural features including the H-bond network distinctive of each form of L-arabitol.

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2. Materials and method

2.1. Instruments

Raman investigations were carried out using a Renishaw InVia Raman spectrometer, composed of a single-grating spectrograph coupled with an optical Leica microscope. The 785 nm line of a Renishaw diode laser was used for excitation. Focusing the laser beam via a ×50 long-working distance objective, a volume of about 400 μm^3 was systematically analyzed. The spectra were collected in backscattering geometry, with a resolution of about 2 cm^{-1} in the 35–3800 cm^{-1} spectral range. During an isothermal transformation Raman spectra were automatically collected in the 35–800 cm^{-1} region, using the wire4.2 software of the Renishaw spectrometer, every 150 s with an acquisition time of 120 s. The 2600–3800 cm^{-1} high-frequency spectrum was analyzed using the 514.5 nm from an Argon laser (Laser 200). Using this incident light, the analyzed volume was 200 μm^3. The temperature dependence of the 2600–3800 cm^{-1} spectrum was performed by collecting spectra with an acquisition time of 120 s by step of 20 K. Spectra were also collected in this high-frequency region during isothermal ageing at T_a = 265 K, with the acquisition time used at lower frequencies.

The high-resolution XY Dilor spectrometer was used to analyze the low-frequency Raman spectra of polymorphic forms of L-arabitol. Using the 514.5 nm line of an argon-krypton Coherent laser, and keeping the slits open at 100 μm, the spectra were collected with an acquisition time of 300 s with a spectral resolution of 1 cm^{-1} in the 10–250 cm^{-1} spectral range.

2.2. Experimental protocol

L-arabitol (purity > 98%) was purchased from Sigma-Aldrich, and used as received. The commercial powder of L-arabitol was sprinkled within an aluminum pan placed on the cold finger of a THMS 600 Linkam temperature device. Fig. 1 shows a picture of the sprinkled powder, taken at room temperature with a X5 microscope objective. More than a dozen droplets were analyzed but only the studies of three of them were reported in this paper, in order to present the different crystallization mechanisms observed in this set of experiments. The powder was heated at 105 °C, i.e. slightly above $T_{m,I}$ = 101 °C, and a distribution of liquid droplets was obtained (Fig. 1) with sizes roughly corresponding to the size distribution of grains in the original sample. These droplets were quenched down to 220 K, maintained at this temperature for 10 min, and then heated at T_a = 265, and 273 K in order to analyze the isothermal crystallization. This thermal treatment was reproduced to analyze the crystallization process in droplets of different sizes at different temperatures T_a. The temperature dependence of the 2600–3800 cm^{-1} spectrum was then analyzed for each polymorphic form. A similar experimental protocol was performed using the XY Dilor spectrometer. Only low-frequency spectra of the undercooled liquid state and forms I and II were taken at 273 K for comparison.

2.3. Data analysis

Isothermal transformations were analyzed using the fitting procedure of Raman bands, available in the wire 4.2 software of the Renishaw spectrometer.

The low-frequency intensity collected using the XY Dilor spectrometer was firstly transformed into Raman susceptibility $\chi''(\omega)$, according to [9,10]:

$$I_{Raman}(\omega, T) = [n(\omega, T) + 1].\chi''(\omega) \quad (1)$$

and

$$\chi''(\omega) = \frac{C(\omega)}{\omega} G(\omega) \quad (2)$$

where C(ω) is the light-vibration coupling coefficient and G(ω) the vibrational density of states (VDOS). The Raman susceptibility is recognized as a close representation of the VDOS, providing the signature of the long-range order in polymorphic phases [11].

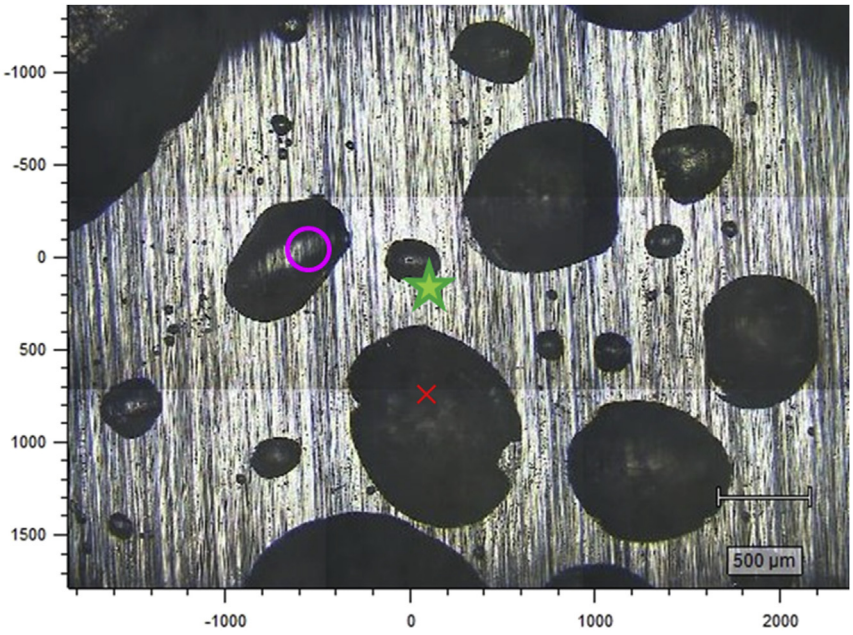

Fig. 1. Picture taken at 273 K after isothermal aging (250 min) of L-arabitol droplets with the X5 objective of Leica microscope coupled with the Renishaw spectrometer. Symbols are used to identify droplets where Raman spectra were collected during the isothermal transformation.