Electronic Supplementary Information

A detailed description of the devitrification mechanism of D-mannitol

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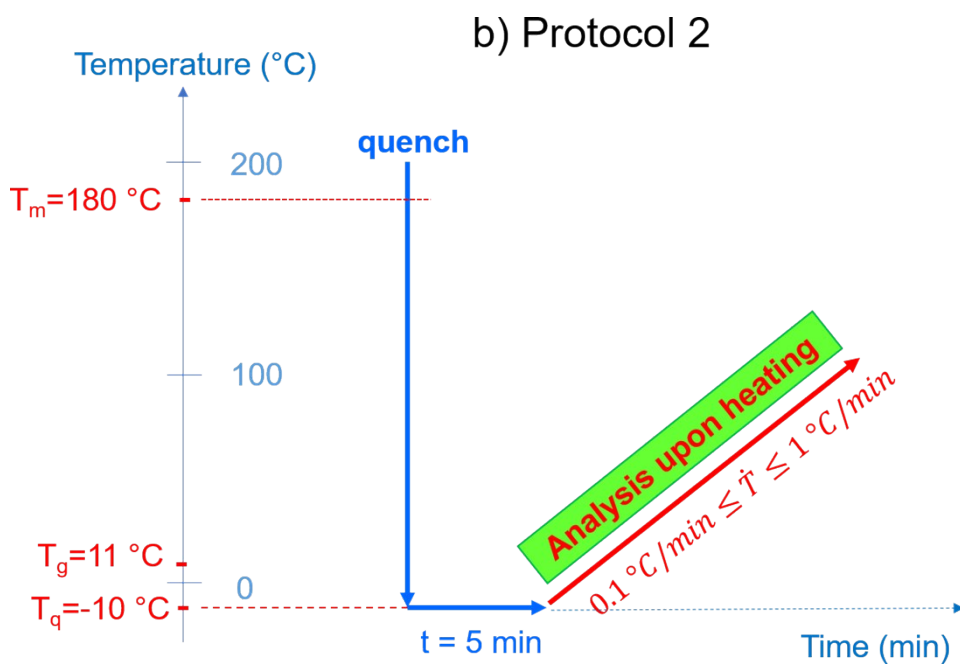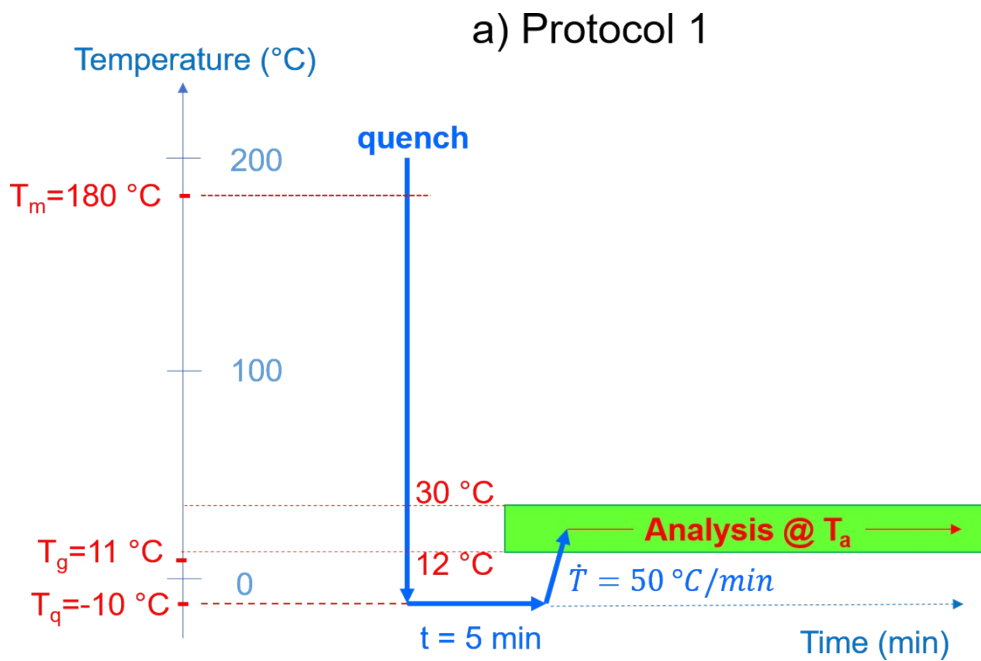
a) Protocol 1

b) Protocol 2

Fig. S1 : description of the thermal history of samples and experimental conditions used for Raman (protocols 1 and 2) and micro calorimetry analyzes (protocol 2).

In protocol 1, liquid mannitol was quenched at -10 °C and heated at 50 °C/min after 5 minutes at -10
°C; spectra were collected during the isothermal aging at several temperatures (T_a)

In protocol 2, liquid mannitol was quenched at -10 °C and heated at various heating rates
($\square^\square$) after 5minutes at -10 °C ; spectra were collected along the heating ramp
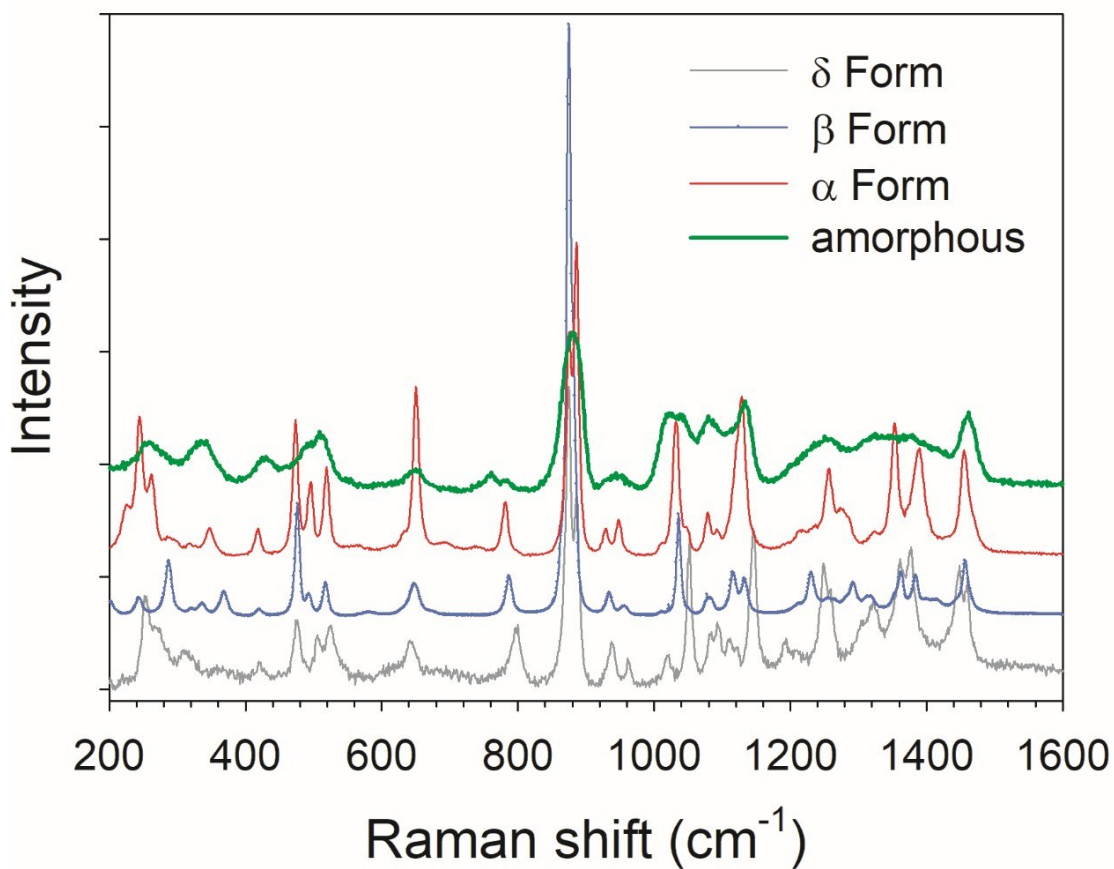
Figure S2: Comparison of Raman spectra in the various crystalline forms and amorphous state of D- mannitol. This figure clearly shows that the crystalline form emerging from the devitrification process can be unambiguously identified by analyzing the whole 200 – 1600 cm^{-1} spectrum.
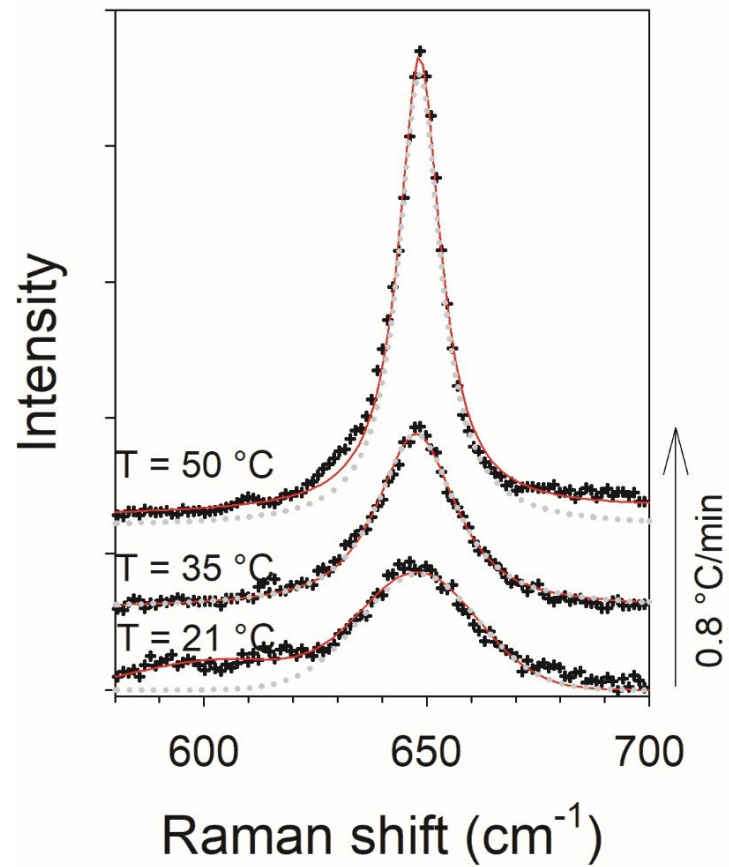
Figure S3: description (at 3 temperatures) of the fitting procedure of the spectrum region around 650 cm^{-1} collected upon heating at 0.8 °C/min using protocol 2. Symbols correspond to the experimental data, red lines to the fitting procedure and dotted grey lines to the mixed Lorentzian-gaussian bandshape used in the fitting procedure

Principal Component Analysis (PCA)

The basic idea of PCA is to represent the original data matrix D by a product of two smaller matrices T and P, respectively the scores matrix and the loadings matrix, according to:

$$D = T \times P^T + E \; (noise) \qquad (1)$$

PCA builds a new coordinate system, called principal components (PC), as a linear combination of the old coordinates. In a set of spectra, spectral features can be considered as a cloud of data points. In this representation spectral modifications can be expressed by a distance between two data points corresponding to a variance. A new coordinate system can be created, the origin corresponding to the centre of the cloud of points, the first axis (PC1) corresponding to the maximum distance between two extreme data points (first maximum variance), the second axis (PC2) corresponding to the second direction of maximum variance, etc. The coordinates of data points in this new axis system are called scores. It can be estimated how much the old coordinates (peaks) contribute to each of the new ones (PCs). These values are called loadings.

The decomposition of a series of *n* spectra, corresponding to relation (1), is shown in a general case in A). A simple example corresponding of a series of 3 spectra is presented in B); in this example the total variance is expressed in 2 PCs defined by the scores plot and their loading. The decomposition of the first spectrum is shown in C).
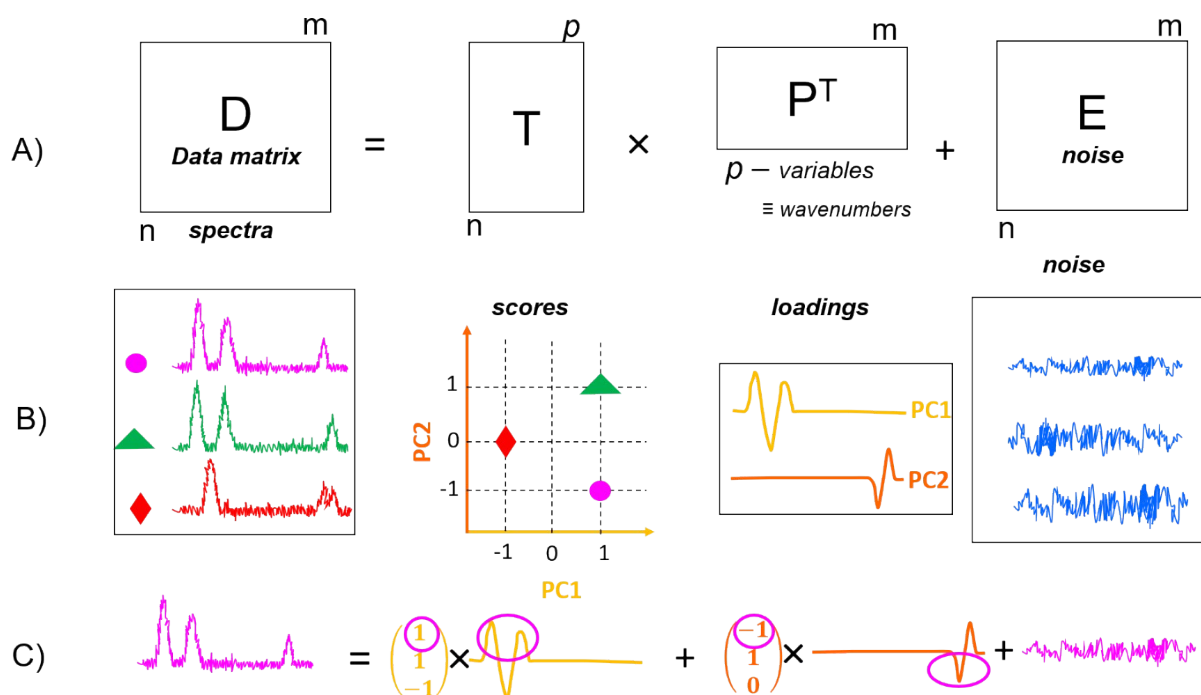
More detailed information about PCA can be obtained in references 23 and 25. Example shown in B) is arising from reference 25 (Smith, G. *et al*. Adv. Drug Deliv. Rev., 2015, 89, 21-41).
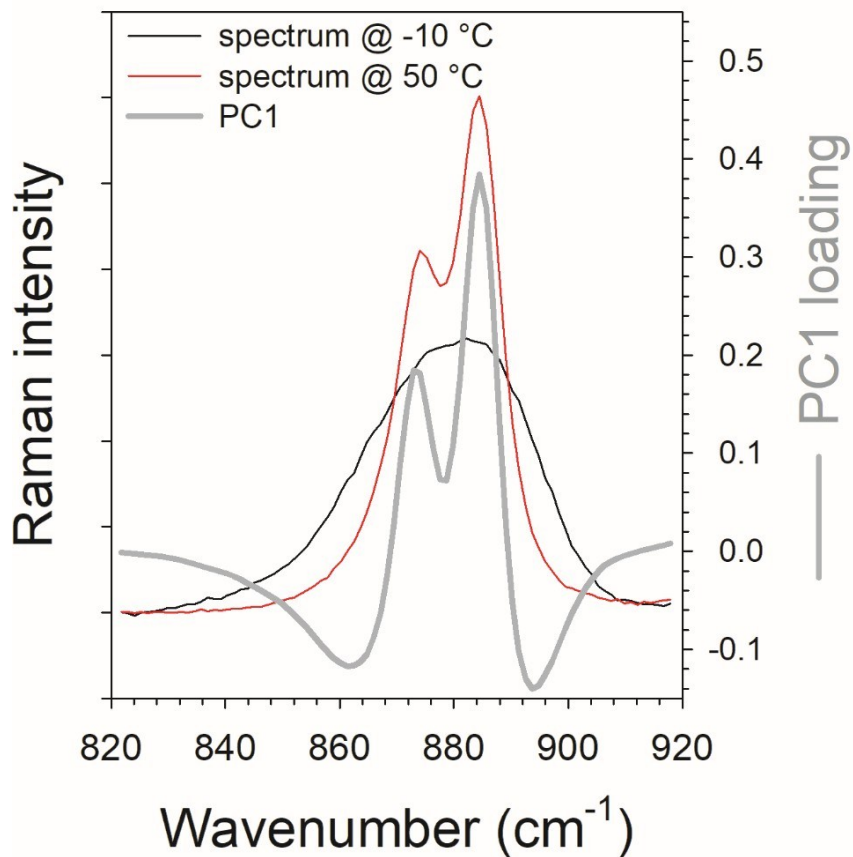
Fig. S4: representation of the loading of PC1 (97.4 %) resulting from PCA of Raman spectra collected during a heating ramp at 0.2 °C/min (protocol 2). Raman spectra were collected using the achromat lens, providing a macroscopic analysis of a droplet. This loading allows the interpretation of spectral changes detected between -10 °C (black spectrum) and 50 °C (red spectrum)
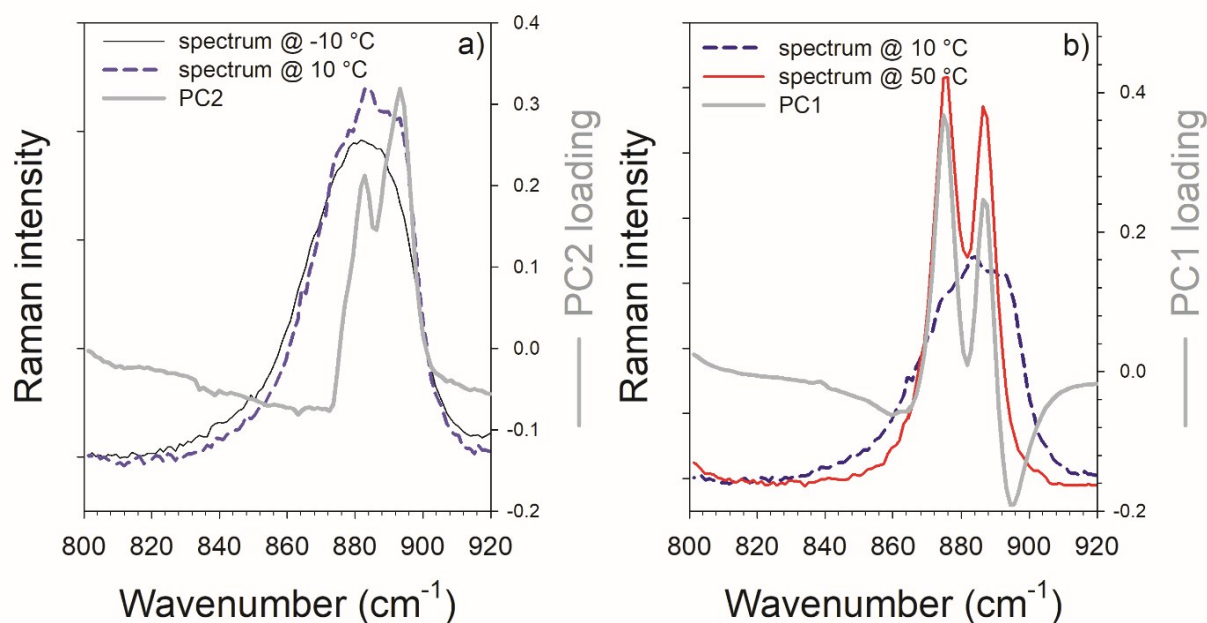
Fig. S5: representation of the loading of : PC2 (4.3 %) a), and PC1 (93.1 %) resulting from PCA of Raman spectra collected during a heating ramp at 0.2 °C/min (protocol 2). Raman spectra were collected using the 50X objective providing a significant contribution of the surface analysis to the Raman signal.

It is observed in Fig. S5a that the loading of PC2 allows the description of the low-temperature transformation between -10 and 10 °C corresponding to the less intense exothermic peak, while Fig. S5b shows that the loading of PC1 mainly described the spectral modifications which occur between 10 and 50 °C corresponding to the two other exothermic peaks.
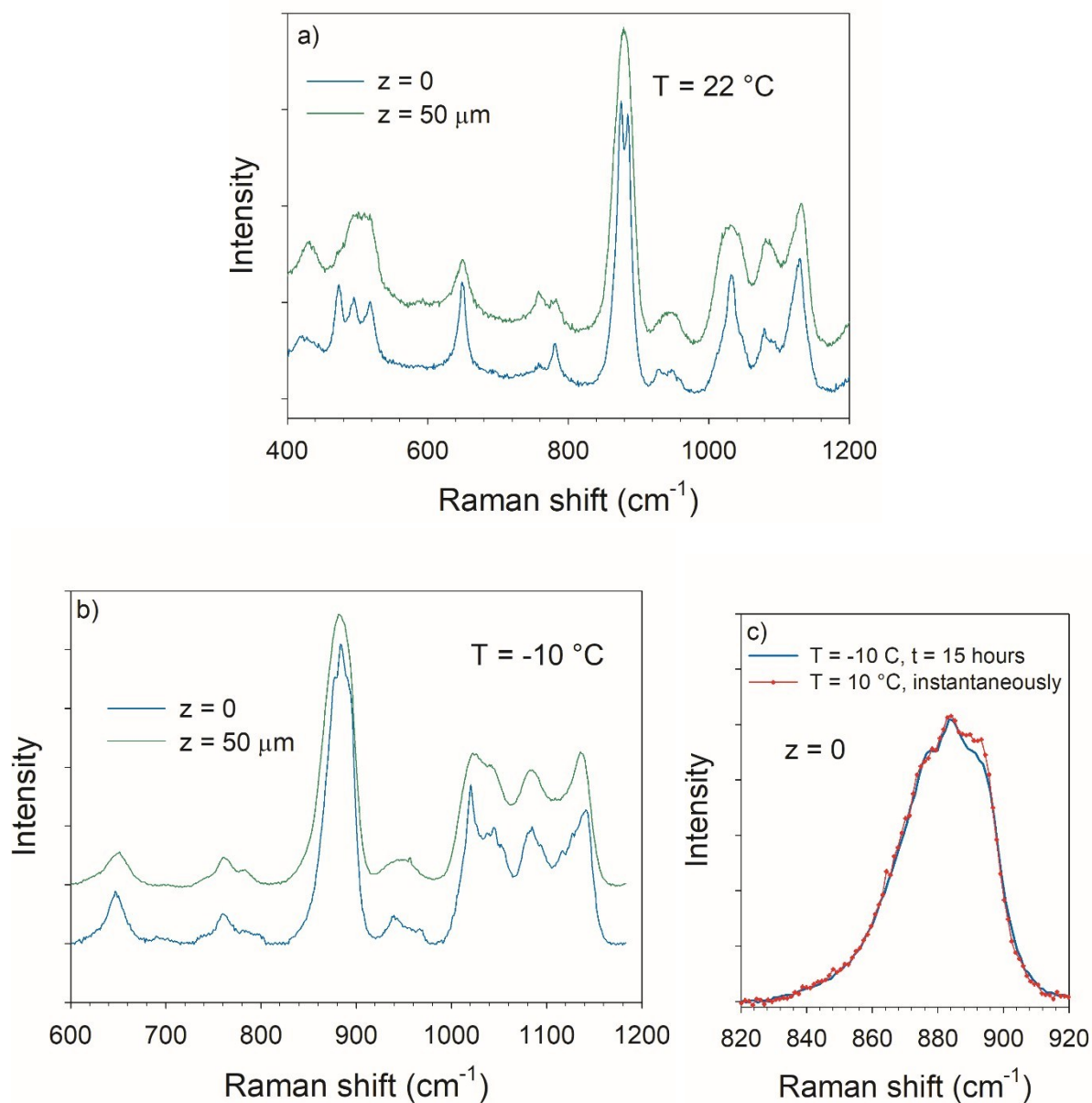
Fig. S6 comparison of Raman spectra taken at various z-position of the XYZ-table of the spectrometer providing Raman spectra at the sample surface (z = 0), and at 50 µm in depth within a droplet of D- mannitol using the 50X objective; spectra are collected after 15 hours of isothermal aging at 22 °C a), at -10 °C (T_g - 21 °C) b); the spectra collected at z = 0, at -10 °C after 15 hours of isothermal aging and instantaneously at ~10 °C upon heating at 0.2 °C/min. The resemblance between these two spectra shows that the surface crystallization is slower than the bulk crystallization and can be detected far below T_g.