Supporting Information:
Selective crystallization of D-mannitol polymorphs using surfactant self-assembly

Frederico Marques Penha,†,‡,¶ Ashwin Gopalan,†,¶ Jochem Meijlink,‡ Fatma Ibis,‡ and Huseyin Burak Eral*,†

†Department of Chemical Engineering, KTH Royal Institute of Technology, Teknikringen 42, SE100-44 Stockholm, Sweden
‡Process & Energy Department, Delft University of Technology, Leeghwaterstraat 39, 2628 CB Delft, The Netherlands
¶These authors contributed equally to this work.

E-mail: h.b.eral@tudelft.nl

Supporting Information Available

The following files are available free of charge.

• Detailed information on Solubility of D-mannitol, Raman characterization, Microscopic characterization, Solubility of SDS, Effect of D-mannitol on the CMC of SDS, Effect of D-mannitol on the solubility of SDS, Induction time measurements and SDS hydrates profile.
Solubility Estimation of Stock D-mannitol

Solubility of the stock D-mannitol was estimated using Crystalline (Technobis®). First, the unaltered D-mannitol powder was analysed using X-Ray Powder diffraction, according to Figure S1. The polymorphic form present in the stock D-mannitol was identified as the \( \beta \) polymorph. Then, samples were submitted to temperature cycles consisted of four steps: a temperature ramp from 5°C to 70°C with a heating rate of 0.1 °C/min, a hold period of 5 minutes at 70 °C, a temperature ramp from 70 textdegree C to 5°C at a cooling rate of 5°C/min, and finally a hold period of 5 minutes at 5°C. All the steps were stirred to ensure uniform mixing. A slow heating rate was employed to accurately find the clear point, while the hold and cooling time were maintained to a minimum to lower the overall experimental time. At least three cycles were performed for each vial simultaneously, enabling statistically reliable data points. The obtained solubility curve can be found in Figure S2.

![Figure S1: X-ray Diffractogram of stock D-mannitol](image)

Figure S1: X-ray Diffractogram of stock D-mannitol

The solubility curve obtained in our work (following the Van’t Hoff equation) is in good accordance with literature data\textsuperscript{S1} for the \( \beta \) D-mannitol. Slight deviations observed can be caused by the experimental methods applied (including optical, gravimetric and conductometric techniques) to identify the clear points. Besides, purity of the stock D-mannitol from different manufacturers can also play a role on the slight solubility variations. The actual solubility value for each temperature used in this work and the corresponding
95% Confidence interval
Solubility of D-mannitol
Literature data
Van’t Hoff fitting

Figure S2: Solubility curve of stock D-mannitol

Literature data can be found in Table S1.

Table S1: Solubility data of β D-mannitol found in this work and literature data

| Temperature [°C] | Concentration [wt/wt %] | Temperature Error [°C] | Temperature [°C] | Concentration [wt/wt %] |
|------------------|-------------------------|------------------------|------------------|-------------------------|
| 12.2             | 15.1                    | 0.8                    | 5.0              | 12.0                    |
| 17.5             | 17.5                    | 0.1                    | 10.0             | 13.0                    |
| 23.4             | 20.1                    | 0.3                    | 15.0             | 14.1                    |
| 30.0             | 24.8                    | 0.1                    | 20.0             | 15.7                    |
| 31.8             | 25.8                    | 0.4                    | 25               | 17.8                    |
| 37.4             | 30.1                    | 0.3                    | 35.0             | 22.8                    |
| 39.7             | 32.1                    | 0.2                    | 40.0             | 25.7                    |
| 41.6             | 33.8                    | 0.5                    | 50.0             | 32.1                    |
| 44.1             | 37.5                    | 0.5                    | 60.0             | 37.9                    |

**Raman characterization**

Raman measurements were obtained for each vial and compared to standards to identify the polymorphic outcome. The Raman standards that was referred to are shown in Figure S3. When a vial displayed several raman shifts that characterize more than one polymorph, it was assigned to be a mixture. An example of a raman spectrum of a mixture is also depicted in figure S3.
Microscopic characterization

Microscopic images taken automatically using in-built Crystalline® camera are shown in Figure S4A. A noticeable impact on the crystal habit of polymorphs can be seen. In absence of SDS, the mixture of polymorphs produced a morphology where the crystals appear to be smaller, and some agglomerates were also observed. This is shown in the Figure S4A. In presence of SDS, polymorphs were found to showcase a characteristic morphology: a needle morphology that was exhibited by all the polymorphic forms of D-mannitol and a platelet morphology selectively exhibited only by the $\beta$-form. The needle morphology suggests that growth is preferred along the axial direction whereas a platelet morphology would be preferred if the growth is favoured both axially and laterally. This is depicted in the Figure S4B and S4C, respectively.

Solubility estimation of SDS

SDS solubility experiments were performed in order to define the temperature and concentration range of the SDS templates. The phase diagram of SDS suggests that it exists either as a monomer, micelle or a hydrated crystal around its Krafft temperature of 16°C. Two
concentrations of SDS were used in our experiments: a concentration well below its CMC to estimate its role as a monomer and a concentration well above its CMC to estimate its role as micelle or a crystal. Since SDS's CMC lies the range of 0.24 wt% to 0.27 wt% at temperatures around krafft point (5 - 25°C), 0.1 wt% was chosen as the concentration below the CMC and 1.22 wt% was chosen as the concentration above the CMC. A small modification to the solubility cycle is introduced in case of SDS experiments. The prepared vials were cooled to 5°C to check for their crystallization. These cooled vials were then subjected to the solubility cycle by heating slowly from 5°C to 30°C. Figure S5 (A-B) depicts the clear vial at 5°C for 0.1 wt% sample and consequently no drop in transmission. Figure S5 (C-D), on the other end, shows the 1.22 wt% sample which precipitates at 5°C and its corresponding clear point when subjected to slow heating.

Effect of D-mannitol on the CMC of SDS

Surface tension measurements were taken for solutions with using the pendant drop analysis on Theta Lite Optical Tensiometer. To study the effect of D-mannitol on SDS properties, the experiments were performed varying the concentration of SDS under constant concentration of D-mannitol (S = 1 at 25 °C) and without addition of D-mannitol. Results can be found on the Figure S6. It can be observed that in presence of D-mannitol, the surface tension of the solution is lower compared to the pure SDS solution. This indicates that D-mannitol is slightly surface active, leading to overall decrease in surface tension. However, the CMC value.
of 8.5 mM is the same in the absence or in the presence of D-mannitol. The low polarity of
the D-mannitol molecules may not be able to provide enough screening effect to reduce or
increase the critical micelle concentration of SDS. This value is also comparable with values
found on literature for the CMC of SDS.\textsuperscript{S4,S5} Hence, it can be concluded that D-mannitol
does not affect the CMC of SDS.

**Effect of D-mannitol on the solubility of SDS**

Conductometry experiments were performed to study the effect of mannitol on the solubility
of SDS. Since D-mannitol is not an ionic molecule and SDS, on the other hand, dissociates
into sulphate and sodium ions, conductivity measurement were used to identify the solubility
of SDS. Metrohm\textsuperscript{®} 914 pH/-Conductometer was used in-situ in a 100 ml glass automated
reactor from Mettler Toledo’s Easymax equipment. Temperature was varied from 10 to 30
\textdegree C in 1 \textdegree C/min rate. The experiments were performed by preparing 1.22 wt\% SDS solution
with and without the presence of S=2.95 D-mannitol solution at 25 \textdegree C.

The results obtained for the conductivity of pure SDS and SDS with D-mannitol concen-
trated solution are depicted in Figure S7. As a common trend, it can be observed that the conductivity value lies flat initially and steeply rises to a higher value around a temperature of 22 °C. This temperature denotes the dissolution of SDS crystals, dissociating to sulphate and sodium ions. In presence of D-mannitol, a slight increase in dissolution temperature is noticed. This could be because of number of reasons: presence of abundant D-mannitol could actually inhibit the dissolution of SDS, or the bulk volume of D-mannitol could render mixing to be ineffective in the equipment and delay SDS dissolution. Due to the closeness of the dissolution temperature, it could be conservatively assumed that mannitol does not affect SDS solubility.

**Induction time measurements**

Figure S8 depicts the probability distribution results obtained for different supersaturated solutions of D-mannitol and SDS. These are pure saturated solutions prepared at different concentrations to identify the nucleation rate. The cumulative probability of nucleation is plotted against time and fitted with Weibull equation (Figure 1) to estimate the induction time:
Figure S7: Variation of conductivity of SDS crystals: A- In absence of D-mannitol, B: In presence of S=2.95 D-mannitol

\[ P(t) = 1 - e^{-\frac{\lambda}{k} d} \]  

(1)

where \( k = \frac{1}{\lambda} \), \( \lambda \) is the induction time and \( d \) is the shape parameter. For \( d = 1 \), the equation reduces to the simple exponential function. For \( d \) values higher or lower than 1, respectively, the nucleation rate is increasing or decreasing with time. It can be observed from the graph that as the supersaturation of D-mannitol increases, the slope becomes steeper and lower is the induction time of the system. S=2.95 solution nucleates at approximately 116 seconds, while S=2.3 solution nucleates the slowest at 867 seconds. Further, the 1.22 wt% SDS solution is found to be closely competing with induction time of S=2.5 D-mannitol solution.

Induction time measurements were also taken for D-mannitol solutions at the higher supersaturation (S = 2.95) containing 0.1 and 1.22 wt% of SDS, to enable the comparison with the nucleation kinetics of pure D-mannitol solutions (Figure S9). An increase in the induction time was observed for the experiment containing 0.1 wt% SDS (444.44 s), indicating slower kinetics compared to pure D-mannitol solutions at the same supersaturation (115.61 s). This can be related to the polymorphic outcome, which, in this condition, is mostly
Figure S8: Cumulative probability distribution of pure solutions of D-mannitol (S = 2.3, 2.5 and 2.95) and SDS with Weibull fitting. Note that the coloured shading around the fit represents the 95 % confidence intervals.

β-D-mannitol. For the condition with 1.22 wt% SDS, for which at 5 °C SDS crystals can form, the induction time was found to be much shorter than for 0.1 wt% (223.71 s) yet still higher than for the solution without SDS. This difference can, once more, be explained in terms of the polymorphic outcome. Pure D-mannitol solutions yielded mostly β and δ mixtures, while the solution containing 1.22 wt% SDS yielded almost 50 % α, known to have slower kinetics. The pure S=2.95 samples were found to nucleate earlier than the samples with 1.22 wt% SDS, owing to the higher percentage of kinetically favoured δ form obtained in the former as compared to the kinetically slower metastable α formed in the latter. Also, the nucleation of pure SDS (472.8 s) is found to be slower than the S=2.5 samples with 1.22 wt% SDS, thus validating the hypothesis that an onset of α is formed because when D-mannitol starts to crystallize, SDS is still in the form of micelles.

**SDS hydrates profile**

SDS crystallizes into an anhydrous form and three hydrated forms being 1/8 hydrate, hemihydrate and monohydrate. In the seeded experiments, both stock and recrystallized SDS crystals were used. The recrystallized and the stock SDS were analysed through XRPD to verify the hydrates profile and how it would affect the polymorphic outcome when used
Figure S9: Cumulative probability distribution of nucleation on D-mannitol solutions ($S = 2.95$) containing varying SDS concentrations with a Weibull fitting. Note that the coloured shading around the fit represents the 95 % confidence intervals.

as seeds. Results are shown in Figure S10. The stock SDS was found to have overlapping peaks with 1/8 hydrate and hemihydrate. This is reasonable as the commercial SDS, which is produced by spray drying, generally consists of a mixture of hydrates. The recrystallized SDS, on the other hand, was found to be of pure 1/8 hydrate. Thus, two types of SDS seeds with different crystal lattices were used in the seeding experiments. Yet, no significant difference on the polymorphic outcome was obtained.

Figure S10: XRPD peaks for stock and recrystallized SDS along with XRPD peaks of anhydrous and hydrated forms of SDS obtained from literature database.
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