Promotion of Mefenamic acid Nucleation by a Surfactant Additive, Docusate Sodium

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SUPPORTING INFORMATION

Mole fraction solubility ratio of polymorphs in different solvents

Representing the free energy difference of a molecule in the solid phases at a certain temperature ($\Delta G^{\text{I-II}}$), the mole fraction solubility ratio $x_A{}^{\text{II}}/x_A{}^{\text{I}}$ is almost independent of the choice of solvent "A", providing that the concentration dependence of the activity coefficient ($\gamma_A(x)$) can be neglected for dilute solutions and thus the ratio of the activity coefficients can be assumed to be 1[1,2]:

$$\Delta G^{\text{II}\to\text{I}} = -kT \ln\left(\frac{a^{\text{II}}}{a^{\text{I}}}\right) = -kT \ln\left(\frac{x_A^{\text{II}} \cdot \gamma_A(x)}{x_A^{\text{I}} \cdot \gamma_A(x)}\right) \cong -kT \ln\left(\frac{x_A^{\text{II}}}{x_A^{\text{I}}}\right) \qquad \text{(eq. S1)}$$

Where a^{II} and a^{I} are the activities of the molecules in the solid phases of Form II and Form I.
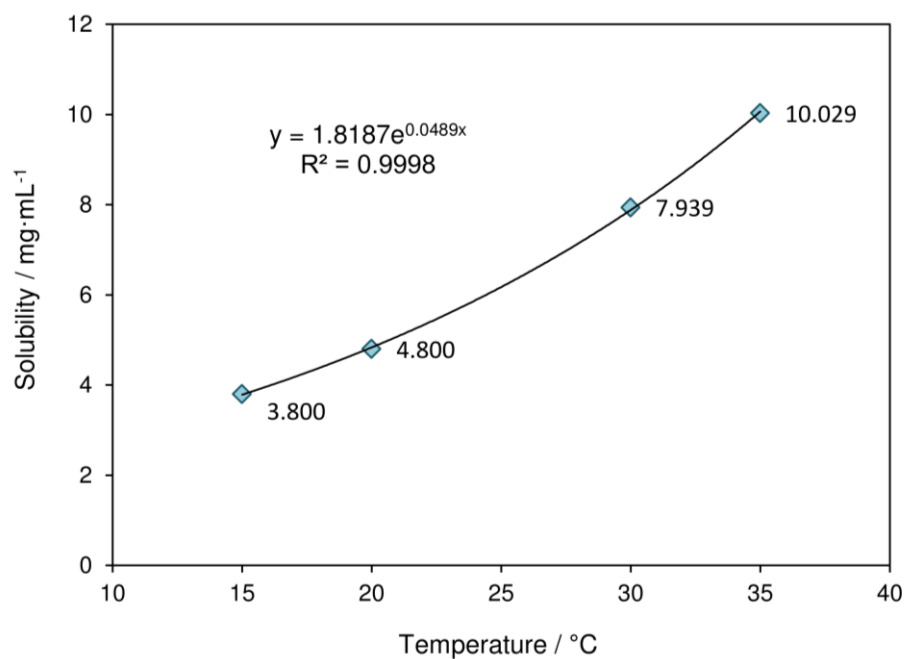
Figure S1 Solubility of MEF Form I in 70 % DMA – 30 % water at 15 °C, 20 °C, 30 °C and 35 °C in the absence of DOSS. An exponential fit to the solubility data is also presented.
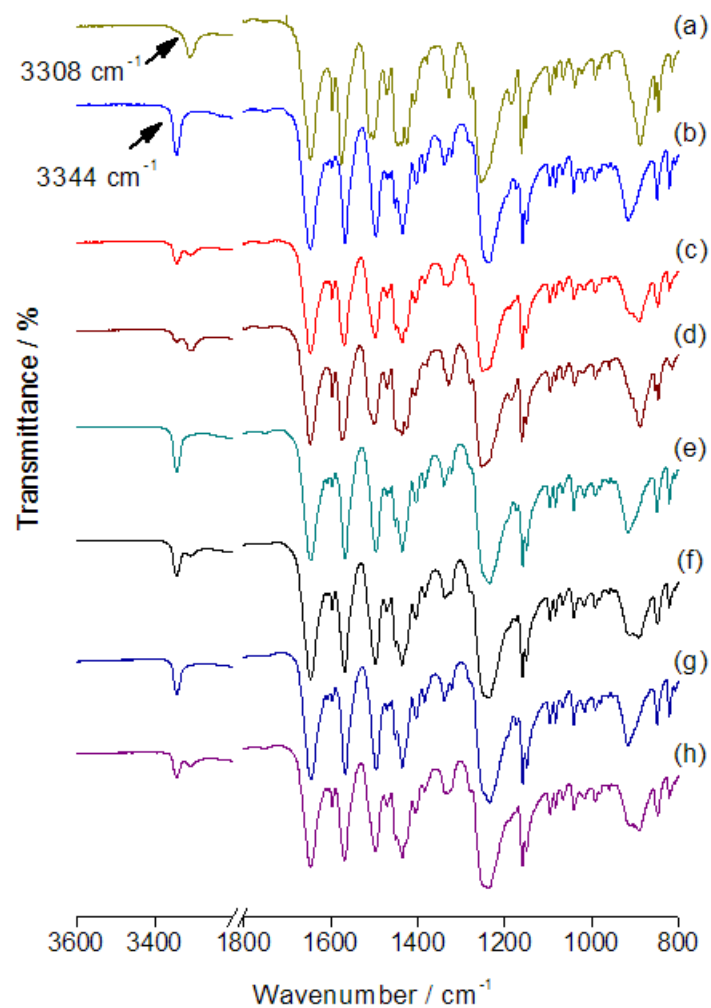
Figure S2 IR spectra of MEF polymorphs: (a) pure Form I, (b) pure Form II; spectra of particles prepared at S^{II}=4.40 (c-d) without DOSS, (e-f) with 0.1 mg/mL DOSS, (g-h) with 0.2 mg/mL DOSS.

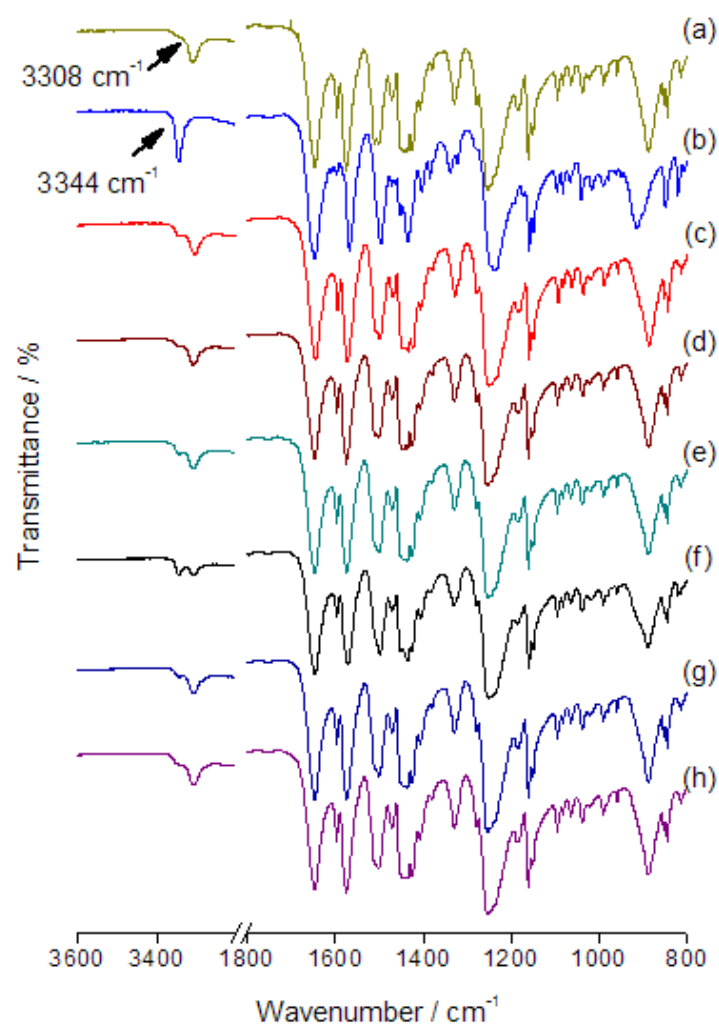Figure S3 IR spectra of MEF polymorphs: (a) pure Form I, (b) pure Form II; spectra of particles prepared at S^{II}=2.20 (c-d) without DOSS, (e-f) with 0.1 mg/mL DOSS, (g-h) with 0.2 mg/mL DOSS. All samples except (d) contained Form II crystals.
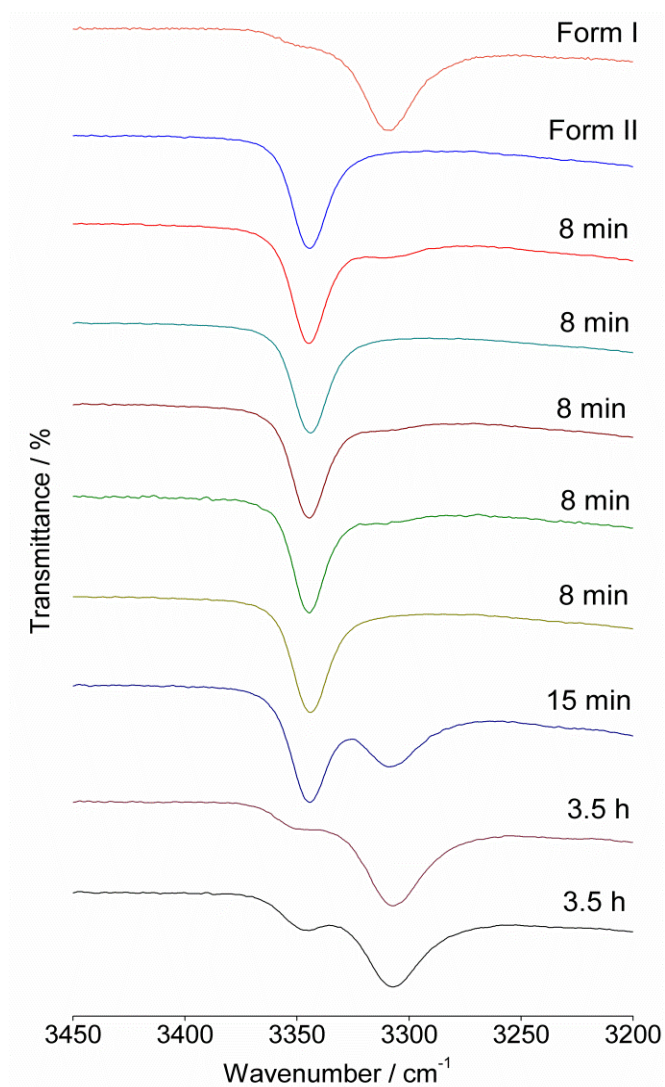
Figure S4 IR spectra of pure MEF polymorphs and MEF crystals nucleated at S^{II} =4.40 in the absence of DOSS, isolated at different times after the detection of crystallization and dried under high vacuum at room temperature. S^{II} is calculated based on the solubility of the nucleating Form II crystals.
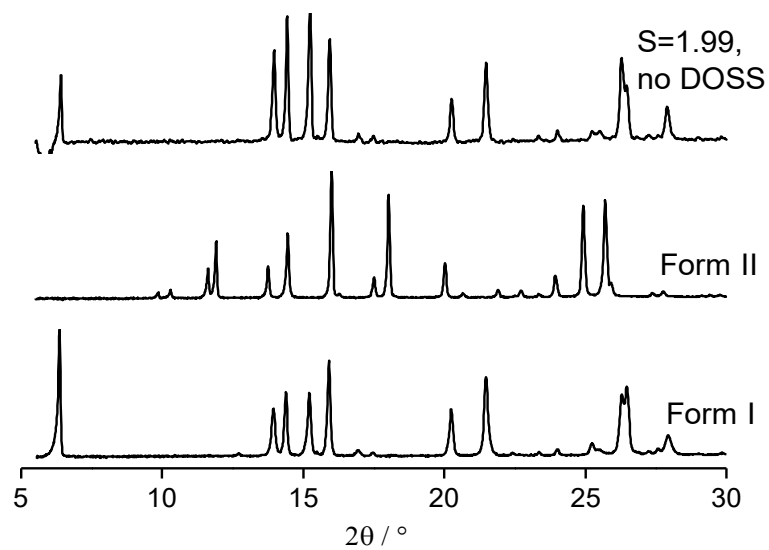
Figure S5 PXRD diffractogram of pure MEF polymorphs and MEF crystals nucleated in 70 % DMA – 30 % water at S^I=1.99 in the absence of DOSS. Crystals were isolated at 8 min aging time.
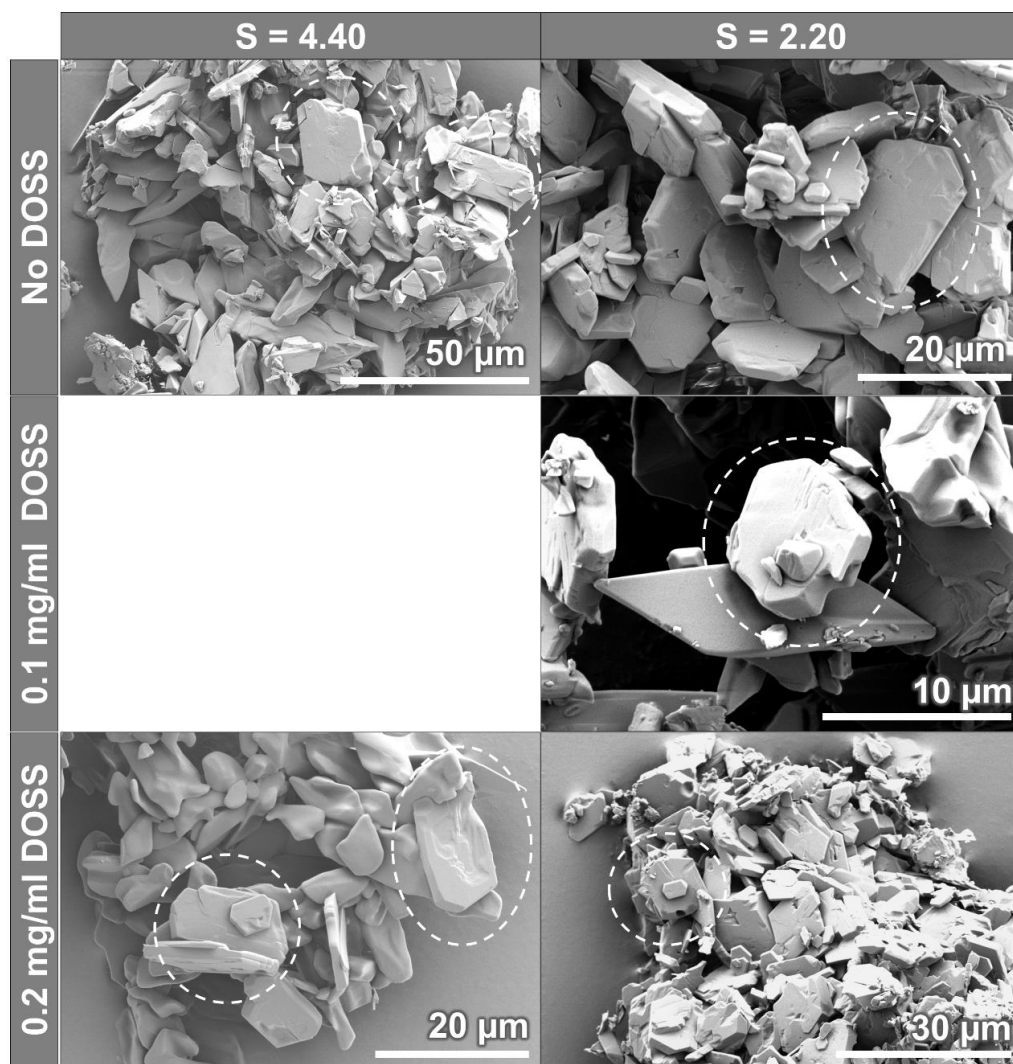
Figure S6 SEM images of MEF crystals prepared in the absence or presence of DOSS in 40 % DMA – 60 % water, at the highest (S^{II}=4.40, isolated at 8 min) and lowest (S^{II}=2.20, isolated at 15 min) employed supersaturation. Based on IR, samples are a mixture of Form I and Form II crystals, except at S^{II}=4.40, 0.1 mg/mL DOSS, with the images showing examples of Form I crystals (circled).
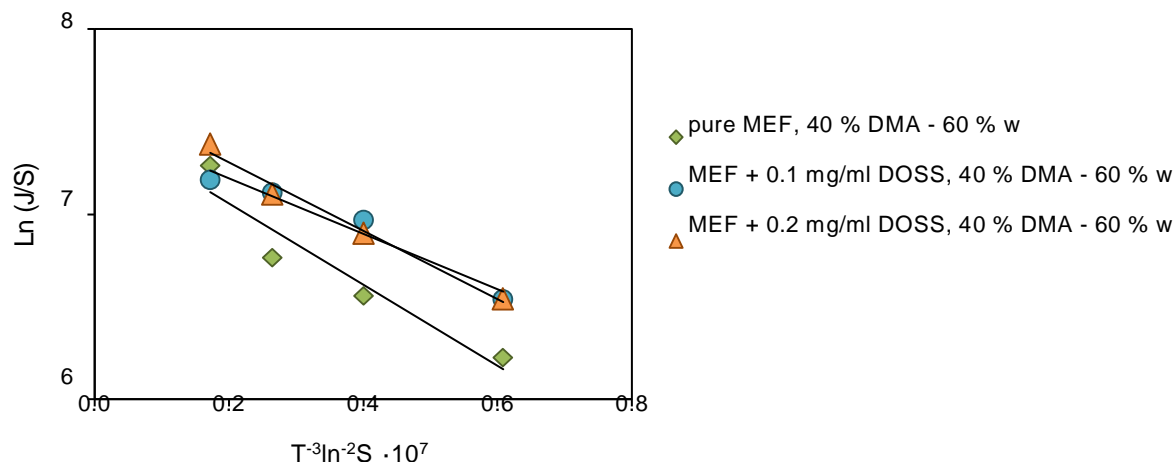
Figure S7 Plot of ln (J/S) versus $T^{-3}\ln^{-2}S$ for the determination of the pre-exponential factor A and interfacial energy γ of the nucleation from fitting to equation (8), including S^{II}=4.40-2.20 in the linear fit in 40 % DMA – 60 % water.

Critical micelle concentration (CMC)

Conductometry was used for determination of CMC of DOSS in deionized water and in 40 % DMA – 60 % water at 25 ˚C. The conductivity of DOSS solutions at different concentrations were measured using a Malvern Zetasizer Nano ZSP and a folded capillary cell (cell type: DTS1070). Prior the measurement, the temperature of the solutions was equilibrated for 10 min at 25 ˚C. The conductivity was measured using three sub-runs and the average was reported as the result. Shown on Figure S8, in pure water, the critical micelle concentration (CMC) of DOSS was 7.8 mM = 3.5 mg/mL. In 40 % DMA – 60 % water, micelles were not detected up to 25 mM = 11.1 mg/mL DOSS, above which the standard deviation of the conductivity values increased significantly, restricting further collection of reliable data points. This means that micelle formation is not expected at 0.2 mg/mL DOSS in 40 % DMA – 60 % water, and on the basis that the CMC of a surfactant generally increases with increasing fraction of organic solvent in a water

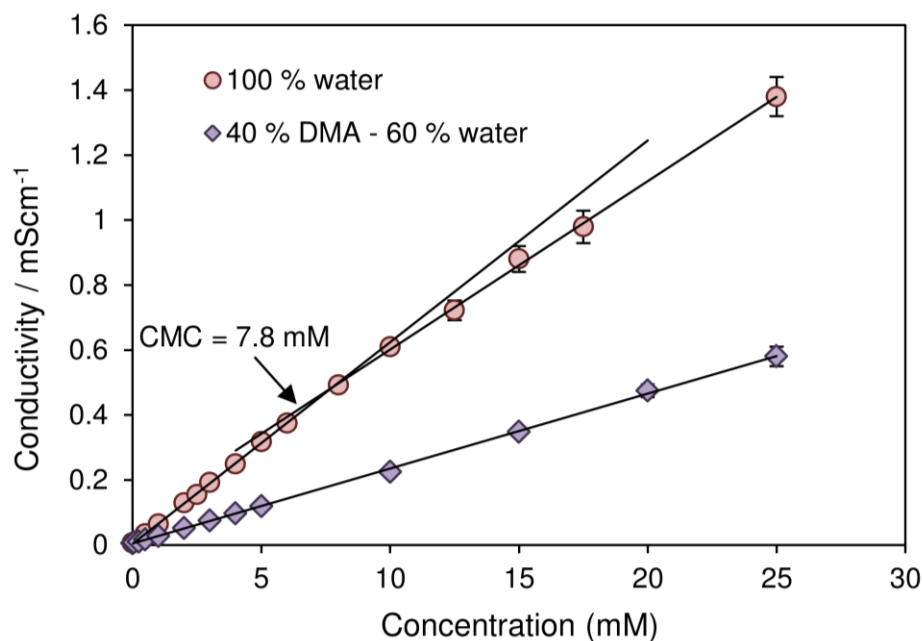– organic solvent mixture[3,4,5], it is also not expected in 70 % DMA – 30 % water even at 5 mg/mL DOSS.

Figure S8 Conductivity of DOSS solutions at 25 °C. The critical micelle concentration (CMC) of DOSS in water is shown as the intercept of the two trendlines.

References

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