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Supporting information for article:

**Bubble-Induced Fast Crystal Growth of Indomethacin Polymorphs
in a Supercooled Liquid**

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Materials

Indomethacin (γ - form) was purchased from Sigma-Aldrich (St. Louis, MO, USA). The model drug was used as received.

Experimental Section

Measurement of Bulk Crystal Growth of IMC polymorph

The crystal growth was tracked by using a polarized light microscope (XP-L2000A, Shanghai Millimeter Precision Instrument CO., Ltd, China) equipped with a hot stage (KEL-X-4A, Shanghai Millimeter Precision Instrument CO., Ltd, China) to achieve temperature control. Briefly, 3-5 mg of crystalline IMC was melted between two clean coverslips at 165°C for 3 min and subsequently quenched to room temperature to form a clear amorphous film. Under the cross-polarized microscope, these samples were confirmed to be amorphous by the absence of birefringence. The thickness of the liquid sandwiched between two coverslips was 15-20 μm . The bulk growth rates of α and γ polymorph were measured with crystals initiated by either spontaneous nucleation or seeding. The seeding experiments were carried out by pushing crystals of α -IMC or γ -IMC into contact with the supercooled liquid to initiate the growth at 100°C, and then the mixtures were transferred to a desired temperature for measuring the crystal growth rates. The seeds of γ polymorph were obtained directly from the purchased IMC raw material. The seeds of α polymorph were crystallized from an ethanol solution upon adding water.

Measurement of Bubble-induced Crystal Growth

To study the crystallization induced by the bubble, the samples were firstly transferred to the desired temperature. Once bubble-induced growth occurred, the growth rates were measured by tracking the advancing speed of a crystal front behind the bubble. The reported growth rates were the average of four independently prepared samples.

Measurement of Surface Crystal Growth of IMC Polymorph

To observe crystal growth at a free surface, 2-5 mg of IMC was melted on a clean 22 mm square coverslip at 165 °C for 3 min, and subsequently covered with a 15 mm diameter round coverslip. After quenching to room temperature, the 22 mm squared cover glass was detached from the IMC sample at 40 °C by gently bending its center toward the round cover glass to expose the free surface. Surface crystal growth rate was measured by tracking the crystals spontaneously nucleated at the free surface. In some studies, surface crystallization was initiated at 40 °C spontaneously, and the sample was transferred to a desired temperature for further measurement. The surface crystal growth was measured under N₂ purge.

Raman Microscopy

A Raman microscope (Thermo Fisher DXR, Madison, WI, USA) equipped with a 780 nm externally stabilized diode laser was used to identify the polymorphism of IMC. Raman spectra were recorded over the wavelength range of 3350–50 cm^{-1} with a resolution of 1 cm^{-1} and an exposure time of 1 s, 20 times, using a laser power of 16 mW. OMNIC software was used to analyze the Raman data.

Shear Viscosity Measurement

The steady shear viscosity of amorphous IMC was measured using an ARES G2 rheometer (TA Instruments, New Castle, DE, USA). Measurements were conducted using two 25 mm diameter parallel plates with a 0.4 mm gap size between them. Nitrogen gas was used to control the temperature inside the heating hood. Briefly, IMC crystalline powders were melted onto the lower parallel plate at 165°C (5 °C higher than the melting point of γ -IMC) for 5-10 min to ensure complete melting. The upper plate was then lowered, and excess material was trimmed off along the border of the plates. After that, the temperature was decreased to a desired temperature. Before shear treatment, the samples were equilibrated at the experimental temperature for 15 min. Then, a shear deformation was applied at a rate of 0.1 s^{-1} to 10 s^{-1} at a constant temperature. The values of shear viscosity were recorded when the shear rate reading become steady. Responses were obtained in term of viscosity (Pa·s) versus temperature (°C).

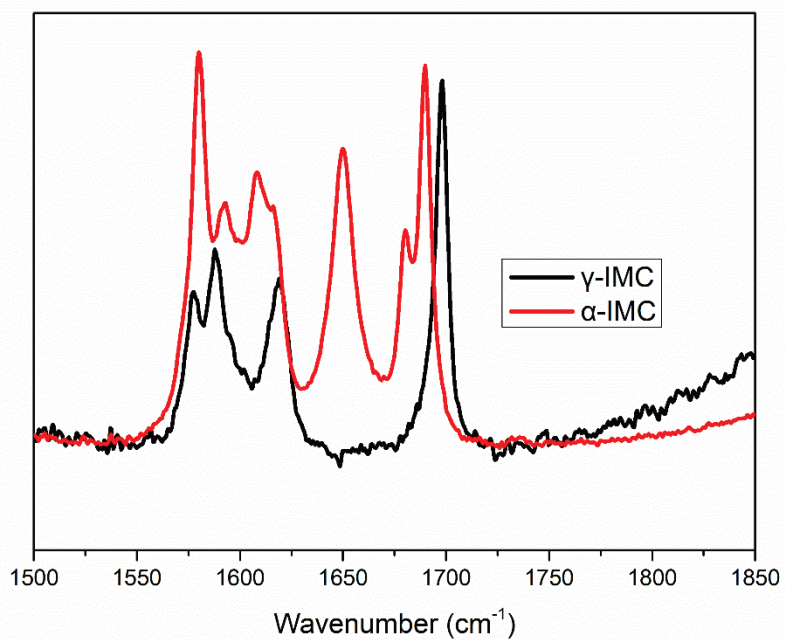


Fig S1. Raman spectra of IMC polymorphs