

Supporting Information

Crystallization of Undercooled Liquid Fenofibrate

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Experimental procedures

Design of the microfluidic nebulator

We produce amorphous fenofibrate using a microfluidic nebulator shown schematically in Figure S1.

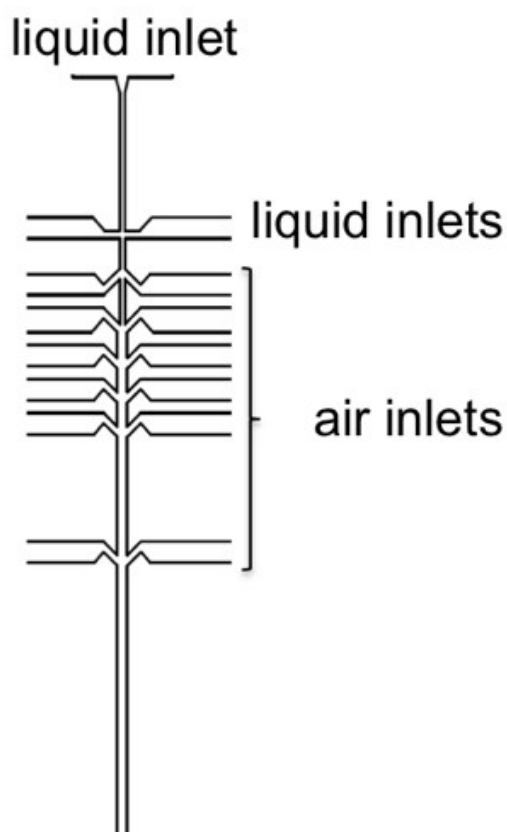


Figure S1: Schematic illustration of the microfluidic nebulator.

Characterization of the nanoparticle size

The size of spray dried nanoparticles was quantified using scanning electron microscopy (SEM). We sprayed nanoparticles onto a one-side polished Si wafer, coated them with a 5 nm thick PtPd layer to make the sample electrically conductive, and imaged them with an Zeiss Supra55VP field emission scanning electron microscope, operated at an acceleration voltage of 2 kV. Images were acquired using the secondary electron detector.

To verify that the size of the undercooled liquid fenofibrate drops remains unaltered during sample preparation and characterization, we also spray dried other organic molecules, such as clotrimazole, under identical conditions. Clotrimazole is a glass at room temperature if amorphous, as its glass transition temperature, T_g , is above room temperature.¹ There were no measurable difference in the size of clotrimazole and fenofibrate nanoparticles, if spray dried under identical conditions,² indicating that the size of fenofibrate nanoparticles is not affected by the sample preparation and SEM analysis.

Differential scanning calorimetry (DSC) analysis

The sample was sprayed into an Al pan which was subsequently hermetically sealed. Differential scanning calorimetry analysis was performed on a TA instrument by heating the sample at a rate of 1 °C/min.

Quantification of the crystal growth velocity

The theory of the crystal growth velocity controlled by multiple layer nucleation has been developed some time ago.^{3, 4} This appendix gives a concise derivation of the equation as used in the text, where most of the quantities have been introduced. The work to form a circular layer ("pillbox") of thickness λ and radius r on a surface is

$w = \pi r^2 \lambda \Delta\mu_v + 2\pi r \lambda \gamma_l$. This work is maximum for $r_s^* = \frac{\gamma_l}{\Delta\mu_v}$ and equals $w_s^* = \frac{\Pi \gamma_l^2}{\Delta\mu_v}$. This

gives an areal concentration of critical nuclei $n_s^* = \frac{1}{\lambda^2} \exp\left(-\frac{w_s^*}{k_B T}\right)$. The corresponding layer nucleation frequency is $I_s = n_s^* k i_s^*$. The lateral spreading velocity of a ledge on a

surface is $v_l = f_l \lambda k \left[1 - \exp\left(-\frac{\Delta\mu}{RT}\right)\right]$. The time required to complete one layer is $\Delta t = \frac{\lambda}{v}$

where v is the bulk crystal growth velocity, normal to the interface. The number of nuclei that form on an interface of area A in that time is $N_s = I_s \Delta t A$. The average area that each nucleus grows in that time is $A_s \approx (v_l \Delta t)^2$. Since in that time the entire area must be covered to complete the layer $N_s A_s = A$ or $I_s \Delta t^3 v_l^2 = 1$. This gives

$v = \frac{\lambda}{\Delta t} = \lambda I_s^{1/3} v_l^{2/3} = (\lambda^2 n_s^*)^{1/3} f^{2/3} i_s^{1/3} k \lambda \left[1 - \exp\left(-\frac{\Delta\mu}{RT}\right)\right]$. The corresponding site factor

for bulk crystal growth is then $f = (\lambda^2 n_s^*)^{1/3} f^{2/3} i_s^{1/3}$. The values of the change in the difference in the chemical potential of a molecule in the crystal and in the undercooled liquid, $\Delta\mu$, the growth velocity of the dendrite tip, v , the jump frequency of the molecule from the liquid to the crystal, k , and the site factor, f , as a function of the undercooling, ΔT , are summarized in Table 1.

Table 1: Temperature-dependent values for the crystal growth of fenofibrate from an undercooled liquid.

T (°C)	ΔT (°C)	η (Pas) ⁵	$\Delta\mu$ (kJ/mol)	v ($\mu\text{m/s}$)	kf (10^3 s^{-1})	k (s^{-1})	f	γ_l (mJ/m ²)
20	60	17	4.89	0.6	0.46	4.48×10^4	1.03×10^{-2}	14
30	50	2.5	4.07	0.8	0.67	3.14×10^5	2.13×10^{-3}	13
40	40	0.7	3.26	1.7	1.61	1.16×10^6	1.39×10^{-3}	12
50	30	0.23	2.45	2.3	2.56	3.65×10^6	7.10×10^{-4}	10

References

1. C. J. Benmore, J. K. R. Weber, A. N. Taylor, B. R. Cherry, J. L. Yarger, Q. Mou, W. Weber, J. Neufeind and S. R. Byrn, *Journal of Pharmaceutical Sciences*, 2013, **102**, 1290-1300.
2. E. Amstad, M. Gopinadhan, C. Holtze, C. O. Osuji, M. P. Brenner, F. Spaepen and D. A. Weitz, *Science*, 2015, **349**, 956-960.
3. S. D. Peteves and R. Abbaschian, *Metallurgical Transactions a-Physical Metallurgy and Materials Science*, 1991, **22**, 1271-1286.
4. A. Kolmogorov, *Izv. Akad. Nauk SSSR, Ser. Math*, 1937, 335-360.
5. J. A. Baird, D. Santiago-Quinonez, C. Rinaldi and L. S. Taylor, *Pharmaceutical Research*, 2012, **29**, 271-284.