Supporting Information

Continuous-Flow, Well-Mixed, Microfluidic Crystallization Device for Screening of Polymorphs, Morphologies, and Crystallization Kinetics at Controlled Supersaturation

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Table of Contents

S1. Momentum Transport in Devices	3
S2. Heat Transport in Thermalizer	4
S3. Mass Transport in Mixer	7
S4. Trajectories of Crystals in Diffuser	9
S5- Governing Equations and Boundary Conditions for Each Device	. 10
S6. Physical Dimensions of 3D Printed Devices	. 19
S7. Screening of o-ABA Crystals in H-shaped Device and Auto-Stop Mechanism in the Cyclone Mixer Design	. 20
S8. Solubility Data of o-ABA	. 21
S9. Estimation of Growth Rates and Size Distribution of o-ABA Crystals in Cyclone Mixer	. 23
S10.Polymorphs of o-ABA at higher Supersaturation in 96-well plate and Cyclone Mixer	. 25
S11.Summary of Screening Results	. 26
S12. Schematic of Proposed Cyclone Mixer for High Throughput Screening	. 27

S1. Momentum Transport in Devices

The momentum balance equation with appropriate boundary conditions was solved to obtain the velocity profiles for each geometry.

$$\underbrace{\rho\left(\frac{\partial u}{\partial t} + u. \nabla u\right)}_{\gamma} = -\nabla p + \underbrace{\nabla \cdot \left(\mu(\nabla u + (\nabla u)^{\mathrm{T}}) - \frac{2}{3}\mu(\nabla \cdot u)I\right)}_{\gamma} + F \qquad \text{Equation 1}$$

$$1 \qquad 2 \qquad 3 \qquad 4$$

where u is the vector of fluid velocity, p is the fluid pressure, ρ is the fluid density, μ is the dynamic viscosity of the fluid, and F is the vector of external forces. The different terms marked in the equation above are respectively defined as inertial forces (1), pressure forces (2), viscous forces (3), and the external forces which are applied to the fluid (4).

Assumptions made to obtain the velocity profile are given below:

- The fluid is incompressible;
- The velocity profile is obtained for 2D flow neglecting the effect of the finite height of the channels to reduce meshing and computation time;
- Flow in the channel is set to be laminar since the calculated Reynolds number for the system is less than 2100;
- No external force other than the gravitational force has been applied to the system;

Applying the aforementioned assumptions, the simplified Navier-Stokes equation would be:

$$\rho\left(\frac{\partial v_x}{\partial t} + v_x \frac{\partial v_x}{\partial x}\right) = -\frac{\partial P}{dx} + \left[\frac{\partial \tau_{xx}}{\partial x} + \frac{\partial \partial \tau_{yz}}{\partial y} + \frac{\partial \partial \tau_{zx}}{\partial z}\right] + \rho_x \qquad \text{Equation 2}$$

where τ is the shear stress, and *v* is the component of velocity vector *u*. The boundary conditions for this system are defined as:

- At walls, no-slip boundary condition, u = 0;
- At the inlet, the average velocity of laminar flow is set as u = u₀, where u₀ varies from 0.2 to 1 ^{cm}/_s;
- At the outlet, the pressure is set to be equal to atmospheric pressure, $P_0 = 1(atm)$

S2. Heat Transport in Thermalizer

The critical length of the thermalizer is one of the design parameters for fabricating the microfluidic devices as discussed in Fig. 1. This critical length allows fluid's temperature inside the channel to reach 99% of the wall's temperature. To obtain critical length, it is required to find the temperature profile of the fluids inside the channel of thermalizer. We solved the Navier-Stokes equation coupled with the energy balance equation (Eq 3) to obtain the temperature profile. The schematic of a thermalizer is shown below:



Figure S1: Temperature profile inside the thermalizer channel with boundary conditions of T_{in} for entering stream and T_{wall} on the walls

We first solve for the Navier-Stokes equation as described in section S1 and then substitute the velocity profile in the energy balance equation below

$$d_z \rho c_p u. \nabla T + \nabla. q = d_z Q + q_0 + d_z Q_p + d_z Q_{vd}$$
 Equation 3

where q is defined as:

$$q = -d_z k \nabla T$$
 Equation 4

and d_z is the width of the channel, T is the temperature, ρ is the fluid density, c_p the fluid heat capacity at constant pressure, k the fluid thermal conductivity, u the fluid velocity field (substituted from the Navier-Stokes equation), and Q is the heat source (or sink). In general, system of the an have heat source, viscous sissipation and pressure work terms.

To simplify the energy balance equation above, several assumptions were considered:

- No external heat source exists in the system;
- The fluid has constant physical properties;

The simplified equation would be then:

$$\rho c_p \left(v_x \frac{\partial T}{\partial x} \right) = -\left(\frac{\partial q_x}{\partial x} + \frac{\partial q_y}{\partial y} \right)$$
Equation 5

The boundary conditions used for solving this system of the equation are:

- At walls, the temperature is fixed, $T = T_{wall} = 70 \text{ °C}$
- At the inlet, the temperature is also fixed, $T = T_{in} = 25^{\circ}C$
- At the outlet, thermal insulation is applied, -n.q = 0

This system of equations was solved for different velocities in the range of 0.2 to $1\frac{cm}{s}$, and different values for the inlet width to obtain the critical length of each set of parameters and presented as a 3D graph in Figure 3. To obtain the relationship (Eq. 1 of artthe icle) between the critical length of the thermalizer, the average fluid velocity and the width of chathe nnel, a data fitting analysis was performed using the curve fitting tool of MATLAB.

The design equation for the thermalizer would then be $l_{th} = 134.3 w^{0.94} v^{1.96}$, where l_{th} is the critical length of the thermalizer, w is the width of the channel and v is the average velocity of the fluid entering the channel. This result compares well with the second order dependence of critical length on the velocity obtained from the analysis of the Graetz problem. To validate the results of the thermalizer and the obtained design equation, the Graetz problem has been explained here as well.

The Graetz Problem considers a steady state heat transfer of a fluid in a channel. The fluids enter the tube with a temperature of T_0 and encounters a wall at ta emperature T_{wall} which is larger or smaller than T_0 . A very simple sketch of this system is shown below:



Figure S2: Schematic of the 2D Graetz problem showing thermalizer channel with boundary conditions of T_0 and T_{wall}

The equation of energy balance in the cartesian frame is used to find the temperature profile.

$$\rho c_p \left(\frac{\partial T}{\partial t} + v_x \frac{\partial T}{\partial x} + v_y \frac{\partial T}{\partial y} + v_z \frac{\partial T}{\partial z} \right) = -\left(\frac{\partial q_x}{\partial x} + \frac{\partial q_y}{\partial y} + \frac{\partial q_z}{\partial z} \right) - \left(\frac{\partial \ln \rho}{\partial \ln T} \right) \frac{DP}{Dt} - (\tau; \nabla v)$$
Equation 6

In this equation, v_x , v_y and v_z are velocity in x, y and z directions and ρ and c_p are the density and specific heat at constant pressure. In order to solve the problem, several assumptions are listed below

- Fully developed laminar flow;
- Constant physical properties of the fluid/incompressible fluid (ρ , μ , k, c_p are constant);
- The two-dimensional problem in x and y direction which means $v_y = v_z = 0$ and velocity in the x-direction is non zero;
- Temperature varies in x and y directions that result in $\frac{\partial T}{\partial z} = \frac{\partial q_z}{\partial z}$;
- Viscous dissipation term is ignored which means $(\tau: \nabla v) = 0$;

Applying all the aforementioned assumptions, the energy balance equation is simplified to:

$$\rho c_p v_x \frac{\partial T}{\partial x} = \left(\frac{\partial q_x}{\partial x}\right) + \left(\frac{\partial q_y}{\partial y}\right)$$
Equation 7
$$\left(v_x \frac{\partial T}{\partial x}\right) = -\alpha \left(\frac{\partial q_x}{\partial x} + \frac{\partial q_y}{\partial y}\right)$$
Equation 8

and $\alpha = \frac{k}{\rho \cdot c_p}$ is the thermal diffusivity of the fluid.

The velocity field is also assumed to have Poiseuille flow, where v_{max} is the maximum velocity at the centerline.

$$v_x(y) = v_{max}(1 - {\binom{y}{W}}^2)$$
 Equation 9

Boundary conditions for solving this equation are then:

- The temperature at the inlet is $T(y, 0) = T_{in} = 25 \text{ °C}$
- The temperature at the walls is $T(W, x) = T_{wall} = 70^{\circ}C$
- At the centerline T (0, x) is finite or $\frac{\partial T}{\partial y}(0, x) = 0$

The reduced energy balance equation becomes

$$v_0(1 - ({}^{y}/{}_{W})^2) \left(\frac{\partial T}{\partial x}\right) = -\alpha \left(\frac{\partial^2 T}{\partial x^2} + \frac{\partial^2 T}{\partial y^2}\right)$$
 Equation 10

It is also required to de-dimensionalize the variables in the governing equation. We define dimensionless variables as:

$$\theta = \frac{T - T_{wall}}{T_0 - T_{wall}}, Y = \frac{y}{W}, Z = \frac{x}{W.Pe}, Pe = \frac{W.v_0}{\alpha}$$

where Z is the dimensionless length, w is of the width of the channel and Pe is the Peclet number. From the two last dimensionless variables, the critical length of the thermalizer can be obtained by substituting valthe ue of Z at θ =0.99 such that

$$z = Z(\theta). w. Pe = \frac{Z(\theta).w^2.v_0}{\alpha}$$
 Equation 11

This equation shows that the critical length of the channel does not change with the wall temperature, however, it varies linearly with the velocity of the fluid and quadratically with the width of the inlet channel. This result compares well with the design equation (Eq. 1 in the article), which further confirms the accuracy of the simulation results.

S3. Mass Transport in Mixer

For designing the mixer, the design parameter chosen is the critical length which is defined as the length at which the outlet stream from the mixer attains the homogeneous concentration, which assures homogenous supersaturation for crystallization. This critical length is calculated from the concentration profile and is considered the length at which the concentration reaches 99% of the well-mixed solution. To get the concentration profile, it is necessary to solve the transport of diluted species coupled with the Navier-Stokes equations for laminar flow. The mole balance equation for the transport of diluted species is given as

$$\frac{\partial c_i}{\partial t} + \nabla . (N_i) = 0$$
 Equation 12

where N_i is defined as:

$$N_i = -D_i \nabla c_i + u c_i \qquad \qquad \text{Equation 13}$$

and c_i is the concentration of solute and D_i is the diffusion coefficient of solute. Following assumptions were made to solve the system of equations:

- The two-dimensional problem in *x* and *y* direction;
- The system has convective as well as diffusive fluxes;
- Diffusion coefficient D_i is assumed to be constant in the system;

These assumptions will simplify the mass balance equation as follows:

$$\frac{\partial c_i}{\partial t} - D_i \nabla^2 c_i + (u. \nabla) c_i = 0$$
 Equation 14

The appropriate boundary conditions for this system are listed as:

• At the walls, no flux boundary condition, $-n.N_i = 0$;

- At the outlet, $-n. D_i \nabla c_i = 0$;
- At the inlet, the concentration for both streams- API and antisolvent are $c_{0,c} = 1$ and 0, respectively;

This system of equations was solved for different velocities in the range of 0.2 to $1\frac{cm}{s}$, and different values for the inlet width to obtain the critical length of each set of parameters and presented as a 3D graph in Figure 4A. To obtain the relationship (Eq. 2 of artthe icle) between the critical length of the mixer, the average fluid velocity and the width of mixthe er, a data fitting analysis was performed using the curve fiting tool of MATLAB.

The design equation for the mixer would be then, $l_c = 3.57 w^{0.99}$, where l_c is the critical length of the mixer and w is the width of the mixer. From this design equation, we can state that the critical length of the mixer varies linearly with the width of the channel and does not depend on the velocity.

Moreover, we have experimentally evaluated the mixing patterns in each device using dye experiments. In each device, pure water stream entered from the left side and the dark blue dye stream was injected from the right side. While the outlet streams were perfectly mixed in a mixer of the T-junction, cross-flow and cell sorter designs, the H-shaped design has a gradient of blue color in the mixer. The steady-state distribution of blue-colored dye are shown below:



Figure S3: Steady-state distribution of blue-colored dye showing mixing in (A) T-junction (B) cross-flow (C) cell sorter and (D) H-shaped designs

S4. Trajectories of Crystals in Diffuser

To find the trajectories of crystals within each of these geometries, the Langevin equation was solved with the Navier-Stokes equations. In this part, we considered all the forces that are applied to the crystals to evaluate their trajectories in the diffuser and to know whether these crystals will flow out from the device or stay inside the trap zone. The Langevin equation was solved considering appropriate external forces-

$$\frac{d(m_p V)}{dt} = F_t$$
 Equation 15

where m_p is the mass of crystal, V is the velocity vector of the crystal, and F_t is the sum of external forces which includes drag force, Brownian force and gravitational force.

The drag force is given as

$$F_d = \frac{1}{\tau_P} m_P (u - v)$$
 Equation 16

where τ_P is characteristic time scale of crystal motion,

$$\tau_P = \frac{\rho_P \, d_P^2}{18\mu} \qquad \qquad \text{Equation 17}$$

 d_p is the diameter of crystal, ρ_P is the density of the crystal, and μ is the average viscosity of the water-ethanol solution. Properties of the crystals are also defined based on the o-ABA which has been used for the experiments.

The other external force is the Brownian force, given as:

$$F_B = \zeta \sqrt{\frac{12\pi k_B \mu T r_P}{\Delta t}}$$
 Equation 18

where ζ is the Gaussian random number with zero mean and unit variance, k_B is the Boltzmann constant, μ is the viscosity, *T* is the temperature and Δt is the time interval for trajectories.

The third force is the gravitational force (in the z-direction) which was included in the Navier-Stokes equation below.

$$\rho(u, \nabla)u = \nabla[-pl + \mu(\nabla u) + (\nabla u)^{\mathrm{T}})] + \underline{F}$$
 Equation 19

The appropriate boundary conditions for this system are listed as:

- Particles were released in the mixer where homogeneous concentration was attained. Release time was set to be at 30 seconds and 10 particles were released;
- The wall condition was set to be 'bounce' which is defined as: $v = v_c 2 (n. v_c)n$ with v_c defined as the velocity of the particle when it is striking the wall;
- The outlet condition was set to 'disappear' since we are storing the coordinates of the particles at each time;

The videos for the simulation of each design are provided in a separate file.

S5- Governing Equations and Boundary Conditions for Each Device

In this section, all the equations and boundary conditions used to obtain velocity, temperature, concentration profiles, and particle trajectories are summarized for each specific geometry. Figure S4 show domain and all the boundaries such as inlets, walls, and outlets which are colored in red, green and blue, respectively. The gray area is the domain in which the differential equations were solved for each device.



Figure S4: 2D schematic of all 5 geometries shown in Fig. 1 with boundaries colored as red for inlet, blue for an outlet, green for walls, and domain colored in gray for (A) T-junction, (B) Crosssection, (C) Cell-sorter, (D) H-shaped, and (E) Cyclone mixer devices.

S5.1- Velocity Profile in Microfluidic Devices

The first step in all the following simulations was to obtain velocity profile within each device using the Laminar Flow module of COMSOL Multiphysics. The velocity profiles were then coupled with heat transfer, mass transfer or particle trajectory module in COMSOL. The boundaries for this problem are marked in Figure S4. The assumptions of the model are listed in section S1. Table S1 summarizes the governing equation and boundary conditions used in this study.

Domain/Boundary	Governing Equation/Boundary Condition
Inlet	The average velocity of laminar flow is set as $u = u_0$
Outlet	The pressure is set to be equal to atmospheric pressure, $P_0 = 1(atm)$
Walls	No-slip boundary condition, $u = 0$;
Domain	Equation 1

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Parameters: Materials selected for all the simulations were ethanol and water and all of the material properties were imported from COMSOL material library. The temperature was set at 25°C in all the models.

Computational Details: The selected mesh type for the T-junction, cross-flow, and cell sorter devices were free triangular meshes with a minimum element size of 0.044 and maximum element size of 0.99. For the H-shaped device, the mesh sizes had a minimum element size of 0.99 μm and maximum element size of 2.01 μm . For the cyclone mixer, the minimum and maximum element sizes of meshes were 146 and 486 μm , respectively. A time dependent study was implemented for a time range of 0 to 10 minutes with a step size of 0.1 minutes. The multifrontal massively parallel sparse direct solver (MUMPS) was used with backwathe rd different formula (BDF) for time integration in all the fluid flow simulations. Relative tolerance was kept at 0.01 and globalthe method was set to be scaled with a tolerance of 10^{-4} . The steady-state velocity profiles are shown in figure S5.



Figure S5: Steady-state velocity profile in (A) T-junction, (B) cross-flow, (C) cell sorter, (D) H-shaped, and (E) cyclone mixer devices. The color bar indicates the magnitude of velocity in m s⁻¹.

S5.2- Temperature Profile in Microfluidic Devices

To calculate the temperature profile in each geometry, the heat transfer module was coupled with the laminar flow module in COMSOL Multiphysics. The boundaries for various geometries are shown in Figure S4. The assumptions of the model are listed in section S2. Table S2 summarizes the governing equation and boundary conditions used in heat transfer simulations.

Domain/Boundary	Governing Equation/Boundary Condition
Inlet	$T(y,0) = T_{in} = 25 ^{\circ}\text{C}$
Outlet	$\frac{\partial T}{\partial x}(y,L) = 0 \text{ or } -n.q = 0$
Walls	$T(W, x) = T_{wall} = 70^{\circ}\text{C}$
Domain	Equation 6

Table S2: Governing Equations and Boundary Conditions to obtain Temperature Profile

Parameters: Materials selected for all the simulations were ethanol and water and all of the material properties have been imported from COMSOL material library. The temperature was initially set at 25°C in all the models at the inlet.

Computational Details: The selected mesh type for the T-junction, cross-flow, and cell sorter devices were free triangular meshes with a minimum element size of 0.044 and maximum element size of 0.99. For the H-shaped device, the mesh sizes had a minimum element size of 0.99 μm and maximum element size of 2.01 μm . For the cyclone mixer, the minimum and maximum element sizes of meshes were 146 and 486 μm , respectively. A time dependent study was implemented for a time range of 0 to 10 minutes with a step size of 0.1 minutes. The multifrontal massively parallel sparse direct solver (MUMPS) was used with backwathe rd different formula (BDF) for time integration in all the fluid flow simulations. Relative tolerance was kept at 0.01 and globalthe method was set to be scaled with a tolerance of 10^{-4} . The steady-state temperature profiles are shown in Figure S6.



Figure S6: Steady-state temperature profile in (A) T-junction, (B) cross-flow, (C) cell sorter, (D) H-shaped, and (E) cyclone mixer devices. The color bar indicates the temperature in °C.

S5.3- Concentration Profile in Microfluidic Devices

The transport of diluted species module and the laminar flow module were coupled in COMSOL Multiphysics to solve for the concentration profiles in microfluidic devices. The boundaries for various geometries are marked in Figure S4. The assumptions of the model are listed in section S3. Table S3 summarizes the governing equation and boundary conditions used in mass transfer simulations.

Domain/Boundary	Governing Equation/Boundary Condition
Inlet	The concentration of o-ABA (solute) in the solvent stream is 1 mol m ⁻³ , and in the antisolvent stream is 0 mol m ⁻³ .
Outlet	$-n.D_i \nabla c_i = 0$
Walls	No flux boundary condition $(-n. N_i = 0)$
Domain	Equation 12

Table S3: Governing Equations and Boundary Conditions to obtain Concentration Profile

Parameters: Materials selected for all the simulations were ethanol and water and all of the material properties have been imported from COMSOL library. The temperature was set at 25°C in all the models. The diffusion coefficient for o-ABA is assumed to be $1 \ge 10^{-9} \frac{m^2}{s}$.

Computational Details: The selected mesh type for the T-junction, cross-flow, and cell sorter devices were free triangular meshes with a minimum element size of 0.044 and maximum element size of 0.99. For the H-shaped device, the mesh sizes had a minimum element size of 0.99 μm and maximum element size of 2.01 μm . For the cyclone mixer, the minimum and maximum element sizes of meshes were 146 and 486 μm , respectively. A time dependent study was implemented for a time range of 0 to 10 minutes with a step size of 0.1 minutes. The multifrontal massively parallel sparse direct solver (MUMPS) was used with backwathe rd different formula (BDF) for time integration in all the fluid flow simulations. Relative tolerance was kept at 0.01 and globalthe method was set to be scaled with a tolerance of 10^{-4} . The steady-state concentration profiles are shown in Figure S7.



Figure S7: Steady-state concentration profiles in (A) T-junction, (B) cross-flow, (C) cell sorter, (D) H-shaped, and (E) cyclone mixer devices. The color bar indicates concentration in mol m⁻³.

S5.3: Crystal Trajectory Profile in Microfluidic Devices

The particle trajectories in different devices were calculated using the particle tracing for fluid flow module coupled with the Laminar flow module in COMSOL Multiphysics. The assumptions of the model are listed in section S4. Table S4 summarizes the governing equation and boundary conditions used in particle tracing simulations.

Domain/Boundary	Governing Equation/Boundary Condition
Inlet	Release time: after $5(s)$
	Initial position; Density: 10 particles per release
Outlet	Disappear; $q = NaN$
Walls	Bounce; $v = v_c - 2 (n. v_c)n$
Domain	Equation 15 with drag, Brownian, and gravitational force

Table S4: Governing Equations and Boundary Conditions to Obtain Particle Trajectories

Parameters: Materials selected for all the simulations were ethanol and water and all of the material properties were imported from COMSOL material library. The temperature was set at 25°C in all the models. The crystals of o-ABA were considered to have a density of $2200 \frac{kg}{m^3}$, and diameter of 300 μm .

Computational Details: The selected mesh type for the T-junction, cross-flow, and cell sorter devices were free triangular meshes with a minimum element size of 0.044 and maximum element size of 0.99. For the H-shaped device, the mesh sizes had a minimum element size of 0.99 μm and maximum element size of 2.01 μm . For the cyclone mixer, the minimum and maximum element sizes of meshes were 146 and 486 μm , respectively. The bidirectionally coupled particle tracing study with the time range of 0 to 360 seconds and time steps of 0.5 seconds was selected to obtain the particle trajectories. The relative tolerance was kept at 10^{-2} and the solver method was generaa lized alpha. The global method was scaled with the tolerance of 10^{-6} . The videos for the crystal trajectories for each design are provided in a separate file.

Calculation of Stokes number: Stokes number is defined as the ratio of characteristic time of the crystal motion to a characteristic time of the flow.

$$Stk = \left(\frac{\tau_p U_0}{d_c}\right)$$
 Equation 20

where U_0 is the average velocity of fluid, d_c is the characteristic diameter of the conduit, and τ_p is the characteristic time of the crystal motion, defined as:

$$\tau_p = \frac{\rho_p d_p^2}{18\mu} \qquad \qquad Equation \ 21$$

Substituting values of density, viscosity, and diameter as listed below,

Density of particle =
$$\rho_p = 2200 \frac{kg}{m^3}$$

Diameter of the particle = $d_p = 300 \ \mu m$
Viscosity of the fluid = $\mu = 0.00109 \frac{N.s}{m^2}$

the characteristic time can be calculated as:

$$\tau_p = \frac{2200 \left[\frac{kg}{m^3}\right] \times (300 \times 10^{-6})^2 [m^2]}{18 \times 0.00109 [\frac{kg.m}{s^2} \cdot \frac{s}{m^2}]} = \frac{198 \times 10^{-6}}{18 \times 0.00109} = 1.1 \times 10^{-2} (s)$$

Now the Stokes number can be calculated as,

$$Stk = \left(\frac{\tau_p U_0}{d_c}\right) = \frac{1.1 \times 10^{-2} [s] \times 10^{-1} \left[\frac{m}{s}\right]}{2 \times 10^{-1} [m]} = 5.5 \times 10^{-3}$$

This is an example of Stokes number calculation for the cyclone mixer. Since d_c is different for dia fferent device, the Stokes number for each device is listed in the table S5. It can be seen that the stokes number is much less than one which indicates crystals follow the streamlines and well dispersed in the bulk of the fluid.

Device	d _c	Stokes number
T-junction	1 <i>mm</i>	1.1×10^{-2}
Cross-flow	1 <i>mm</i>	1.1×10^{-2}
Cell Sorter	1 <i>mm</i>	1.1×10^{-2}
H-shaped	1 <i>mm</i>	0
Cyclone mixer	2 <i>mm</i>	5.5×10^{-3}

Table S5: Stokes Number for Different Microfluidic Device

Calculations of settling velocity:

Although the lower Stokes number confirm that crystals are well dispersed in the bulk of the fluid, the crystals nucleating and growing near the wall where the fluid velocity is negligible can settle. The following formula can be used to calculate the settling velocity for the case when $Re \leq 2 \times 10^{5}$.¹

$$W_{s} = \frac{v}{d_{p}} d^{*3} \left[38.1 + 0.93 d^{*} \left(\frac{12}{7} \right) \right]^{-\frac{7}{8}}$$
 Equation 22

whereas v is the fluid kinematic viscosity, d_p is the average size as $300\mu m$, and d^* is the dimensionless crystal diameter defined as:

$$d^* = \left(\frac{\Delta g}{v^2}\right)^{\frac{1}{3}} d_p$$
 Equation 23

where $\Delta = \frac{\rho_s}{\rho} - 1$, and ρ_s and ρ are particle and fluid density, respectively, and g is the gravitational acceleration. To calculate the value for W_s the density and kinematic viscosity of ethanol: water (1:1) mixture at room temperature were considered.

The dimensionless diameter of the particle, d^* will be:

$$d^* = \left(\frac{1.463 \left[\frac{kg}{m^3}\right] \times 9.807 \left[\frac{m}{s^2}\right]}{1.287 \times 10^{-6} \left[\frac{m^2}{s}\right]}\right)^{\frac{1}{3}} \times (300 \times 10^{-6} [m]) = 6.162$$

$$W_{s} = \frac{1.287 \times 10^{-6} \left[\frac{m^{2}}{s}\right]}{300 \times 10^{-6} [m]} \times 6.162 \times \left(38.1 + 0.93 \times 6.162^{\frac{12}{7}}\right)^{-\frac{7}{8}} = 2.8278 \times 10^{-2} \left[\frac{m}{s}\right]$$
$$= 2.8278 \left[\frac{cm}{s}\right]$$

The settling velocity was higher than the maximum velocity of the fluid in the cyclone mixer, which was obtained from COMSOL simulations and listed in Table S6.

Table S6: Maximum Velocity in the Cyclone Mixer for Different Inlet Velocities

Inlet Velocity $\left[\frac{cm}{s}\right]$	Maximum velocity in the cyclone before the outlet $\left[\frac{cm}{s}\right]$
0.1	0.19412
0.2	0.38811
0.3	0.58197
0.4	0.7757
0.5	0.96929
0.6	1.1628
0.7	1.3561
0.8	1.5993
0.9	1.7423
1	1.93

S6. Physical Dimensions of 3D Printed Devices

All the dimensions for 3D printed devices that are shown in Fig. 1 are listed in Table S7. The cross-section of channels in the devices is given by $W \times H$ and the length of the channels is denoted as *L*.

Table S7: Dimensions of 3D Printed Microfluidic Devices in Fig. 1. Length is denoted as L
Width is denoted as W, Height is denoted as W, and Diameter is denoted as D.

Device	Thermalizer	Mixer	Diffuser
T-junction	L = 10 mm	L = 10 mm	L = 21 mm
	W = 1mm	W = 1mm	W = 1mm
	H = 1mm	H = 1mm	H = 1mm
Cross-flow	L = 10 mm	L = 10 mm	L = 21 mm
	W = 1mm	W = 1mm	W = 1mm
	H = 1mm	H = 1mm	H = 1mm
Cell Sorter	L = 10 mm	L = 10 mm	L = 10 mm
	W = 1mm	W = 1mm	W = 1mm
	H = 1mm	H = 1mm	H = 1mm
			D = 3 mm
H-shaped	L = 10 mm	L = 1 mm	L = 10 mm
	W = 1mm	W = 1mm	W = 1mm
	H = 1mm	H = 1mm	H = 1mm
Cyclone Mixer	L = 10 mm	D = 4 mm	L = 10 mm
	W = 1mm	H = 4 mm	W = 1mm
	H = 1mm		H = 1mm

S7. Screening of o-ABA Crystals in H-shaped Device and Auto-Stop Mechanism in the Cyclone Mixer Design

Figure S8 shows the variation in morphology and number density of o-ABA crystals along the length of the mixer in the H-shaped device. The crystals were grown at a supersaturation of 1.9 by feeding a saturated solution of o-ABA in ethanol through the left channel and the antisolvent water through the right channel such that an average volume fraction of water is 0.5 (which corresponds to S = 1.9 according to solubility diagram in Fig. S11) at the center of the mixer. Since the supersaturation increases with increasing the volume fraction of water (antisolvent), the gradient in the volume fraction of water (see Fig. S7 D) causes the gradient in supersaturation, which in turn, results in higher nucleation and growth of o-ABA on right (water side) compared to the left (ethanol side). Due to variation in supersaturations, the crystal morphology, as well as polymorphs, also vary along the length of the mixer of H-shaped device. Such variation can be minimized using a shorter length of the mixer and slower growing crystals such as proteins and metal-organic framework. Comparing Figure S8 with Figure 6, it is evident that the cyclone mixer is a better design to screen morphology and polymorphs of crystals at constant supersaturation.



Figure S8: Schematic of the H-shaped design used for o-ABA crystallization at the supersaturation of 1.9. The optical images are obtained at three different locations in the passive mixer of the H-shaped design - (A) ethanol (solvent) side, (B) middle of the mixer, (C) water (antisolvent) side. The variation in crystal number density and size along the mixer is due to supersaturation gradient.

The constant supersaturation conditions in the H-shaped and cyclone mixer designs allow crystals to grow continuously in the mixer compartment. The growing crystals eventually fill the mixer and block all the inlets to stop the crystal growth and screening study. This auto-stop mechanism is a unique feature of these devices that permit unmonitored control of polymorph screening. Figure S9 shows the cyclone mixer design filled completely with the crystals of o-ABA at the end of the screening study, which can also be extracted for further characterization.



Figure S9: Crystals of o-ABA grown at the constant supersaturation inside the cyclone mixer. The crystals eventually fill the mixer and block the inlets that automatically stop crystallization.

S8. Solubility Data of o-ABA

The solubility curves and phase diagrams were obtained from Jiang et al. Figure S10 shows the solubility of form I (solid blue line denoted as c_{II}^*) and form II (solid red line denoted as c_{II}^*) as a function of volume fraction of water in the water-ethanol mixture. For a given concentration (black solid line denoted as c), the supersaturations for form I (dashed blue line denoted as S_I) and form II (dashed red line denoted as S_{II}) were obtained using the solubility curves. Figure S11 shows dominant polymorphs of o-ABA at different supersaturations. It can be seen that form I and form II are dominant at supersaturations < 1.3 and > 1.8, respectively.



Figure S10: Solubility curves of *o*-ABA as a function of water volume fraction at 298 K. (\blacktriangle) form I; (\blacksquare) form II. Solid Lines (c^*_{II} and c^*_{II}) are trendlines of both forms. The trendline of c^*_{II} was estimated with the value of $c^*_{II}/c^*_{I} = 1.20$ at $x_{v,w} = 0.6-0.8$. Solid-straight line (*c*) shows the working line as a function of water volume fraction. Dashed lines are supersaturations S_{I} and S_{II} determined by the ratio between the working line and the solubility curves of both forms under the assumption of perfect mixing. (*Published in: Shanfeng Jiang; Joop H. ter Horst; Peter J. Jansens; Crystal Growth & Design 2008, 8, 37-43., DOI: 10.1021/cg070517n, Copyright* © 2008 American Chemical Society)



Figure S11: Polymorphs identified just after the first appearance of crystals using microscopy as a function of the initial supersaturation ratio S_{I} and water volume fraction $x_{v,w}$. Interfacial energy γ increases with increasing $x_{v,w}$ from 19.2 to 30.0 mJ/m². (*Published in: Shanfeng Jiang; Joop H. ter Horst; Peter J. Jansens; Crystal Growth & Design* **2008**, *8*, 37-43., DOI: 10.1021/cg070517n, Copyright © 2008 American Chemical Society)

S9. Estimation of Growth Rates and Size Distribution of o-ABA Crystals in Cyclone Mixer

The time-lapsed images of crystal growth can also be processed to estimate growth rates at constant supersaturation. Figure S12 shows the time-lapsed images of form I of o-ABA crystals taken at every 30 secs while growing at a supersaturation of 1.2. The images were analyzed using OLYMPUS stream images analysis software to measure the distance between two parallel faces and the growth rate of faces was then calculated to be 0.63 μ m s⁻¹.

Fig. S13 shows the size distribution of o-ABA crystals in Fig. 6B obtained using image processing toolbox of MATLAB. The average size of form I crystals of o-ABA grown for 60 secs at S = 1.2 was 40 µm.



Figure S12: Time-lapsed images of o-ABA crystals (form I) taken at every 30 secs while growing at a supersaturation of 1.2 in a cyclone mixer. The distances between two parallel faces of o-ABA crystal are also reported in the images.



Figure S13: Size distribution of o-ABA crystals of form I obtained after 60 secs at S =1.2. This size distribution was obtained by processing Fig. 6B.

S10.Polymorphs of o-ABA at higher Supersaturation in 96-well plate and Cyclone Mixer

Figure S14 shows the results of screening of o-ABA crystals at a higher supersaturation ratio of 2.5 in 96-well plate and cyclone mixer design. Initially form II appeared in the 96 well plate (Figure S14 A), which then gradually transformed to form I (Figure S14B) after 5 mins due to depletion of supersaturation. In contrast, the cyclone mixer was able to grow the metastable form II throughout the course of the experiment (see Figure S14 C and D). The polymorphs were confirmed with measured XRD patterns shown in Figure S14E.



Figure S14: Screening of o-ABA crystals at a higher supersaturation ratio of 2.5 in 96-well plate and cyclone mixer. (A) Needle-like crystals of form I observed in the 96-well plate after 60 seconds. (B) Crystals in the 96 well plate after 360 seconds showing some of the form II crystals transformed to form I (prismatic morphology) (C) Needle-like crystals observed in the cyclone mixer after 60 seconds. (D) More needle-like crystals observed in the cyclone mixer after 360 seconds. (F) XRD patterns of extracted needle-like crystals confirming form II polymorph of o-ABA.

S11.Summary of Screening Results

Table S8 and S9 summarize the results of the screening experiments after 3~5 minutes at different superstations in the cyclone mixer as well as 96-well plate devices, respectively.

Table S8: Summary of Experimental Screening Results using Cyclone Mixer

Supersaturation	Polymorph	Morphology	Average	Growth	Stability
			Particle Size	rate	
1.2	Form I	Prismatic	40µm	$0.63 \frac{\mu m}{s}$	Stable
1.9	Form II	Needle-like	550µm	-	Stable
2.5	Form II	Needle-like	630µm	-	Stable

Supersaturation	Polymorph	Morphology	Average	Growth	Stability
			Particle Size	rate	
1.2	Form I	Prismatic	34µm	$0.63 \frac{\mu m}{s}$	Stable
1.9	Form I and II	Prismatic	43µm	-	Unstable
		Needle-like	$310 \mu m$		
2.5	Form I and II	Prismatic	48µm	-	Unstable
		Needle-like	370µm		

Table S9: Summary of Experimental Screening Results using 96-Well Plate

S12. Schematic of Proposed Cyclone Mixer for High Throughput Screening

Figure S15 shows the schematic of a high-throughput system using parallel cyclone mixer devices. The inner circle in the central feed of the API solution to various cyclone mixer and the outer circle feed antisolvent at different flowrates to cyclone mixer to generate different supersaturation. The blue color channels represent thermalizers, the green compartment in the mixer, and the yellow section is the diffuser.



Figure S13: High-throughput system for parallel screening of polymorphs and morphology using four cyclone mixers each operating at a different supersaturation.

References

(1) Zhiyao, S.; Tingting, W.; Fumin, X.; Ruijie, L.: A simple formula for predicting settling velocity of sediment particles. *Water Science and Engineering* **2008**, *1*, 37-43.