Electronic Supplementary Material (ESI) for CrystEngComm

Supplementary information

Microfluidic Approach to Polymorph Screening through Antisolvent Crystallization

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Further Details on Chip Design and Operation

A schematic of a single well is shown in Figure S1. Each well has a 'width' of 750 µm and a total 'length' of 1 mm. The 'lengths' of the two compartments within the well, the antisolvent and the API solution chamber, are changed across the chip such that the antisolvent-to-solution ratios (L_{AS}-to-L_{API}) are 50:10, 44:16, 39:21, 33:27, 27:33, 21:39, 16:44, and 10:50. The height of the control and fluid lines are 50 µm within PDMS layers with a thickness of 70 µm.

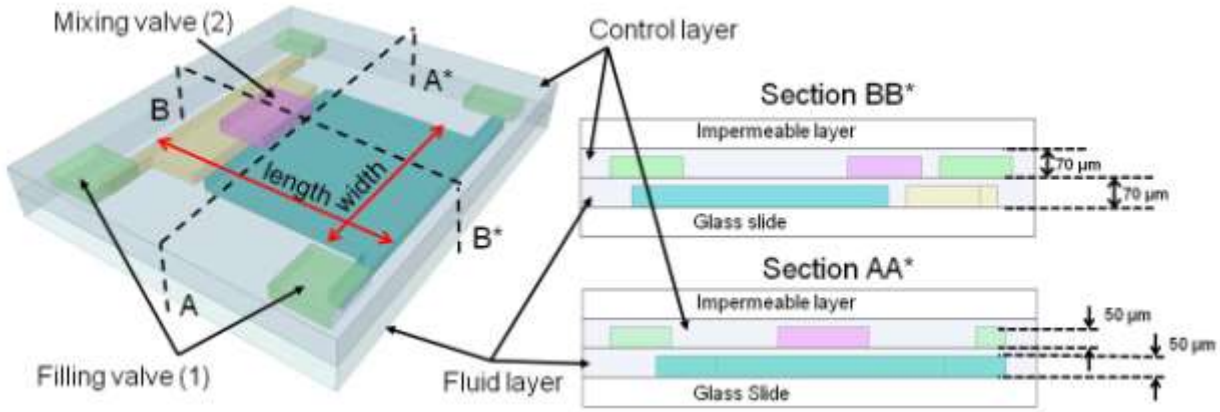

Figure S1. Schematic side view of an individual well within the microfluidic platform with two side views.

Two valve sets control fluid movement. Specifically, the 'filling valve' (Figure S1) enables vertical filling of the API solutions and antisolvent in parallel (Figures S2) and the 'mixing valve' (Figure S1) initiates mixing between the API and antisolvent chambers in each well (Figures S2). This process can be visualized in Figure S2.

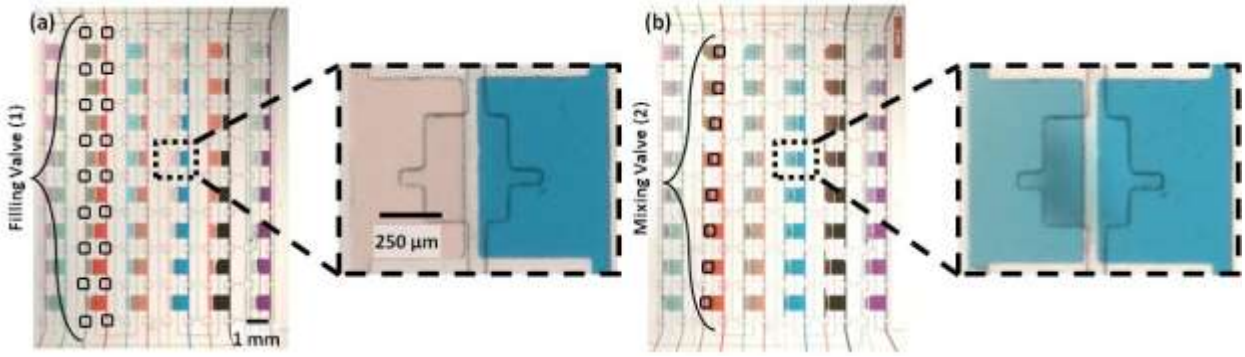

Figure S2. Optical micrographs (a) shortly after filling of solutions and (b) during mixing of solutions within the antisolvent and API solution chambers. Valve 1 controls the filling of the solutions and valve 2 controls the mixing of the solutions

Further Details of the Modeling Process

A 2D, rather than 3D, geometry was modeled because the diffusion profiles are independent of the channel height. Furthermore, a 1D geometry would not have accounted for the two-dimensional diffusion around the valve separating the API solution and antisolvent chambers.

The dimensions of the model are identical to the dimensions of the wells within the actual chip. Specifically, the width (y-axis in Figure S1) of both the API solution chamber and the antisolvent chamber was 750 µm. The combined length (x-axis in Figure S1) of the API and antisolvent chambers was 950 µm. Furthermore, the width of the API solution chamber (L_{API}) and the width of the antisolvent chamber (L_{AS}) were changed such that the L_{AS}:L_{API} ratios modeled were 50:10, 44:16, 39:21, 33:27, 27:33, 21:39, 16:44, and 10:50. The API and antisolvent chambers were separated by a mixing valve 500-µm wide (y-axis in Figure S1) with a length of 50 µm (x-axis in Figure S1), as seen in figure S1.

To model the diffusion of the API, a dilute species, we employed the COMSOL module, "Transport of Dilute Species", which uses a simplified version of Fick's law.

$$\frac{\partial C_1}{\partial t} + \nabla \cdot (-D_1 \nabla C_1) = 0$$

The initial concentration of indomethacin was 15 mg/mL. The diffusion of Indomethacin was assumed to be isotropic and the diffusivity in solution was assigned as 5.6×10^{-6} cm/s[2].[1] We ignored the influence of different solvents on the diffusivities of the APIs due to limitations in the physical data.

To accurately model the diffusion of methanol and water, we accounted for changes in the density based on the composition of the mass fraction of methanol in the solvent. This required using a more complicated module, "Transport of Concentrated Species", which uses a more complete version of Fick's law.

$$\rho \frac{\partial \omega_i}{\partial t} + \nabla \cdot (-(\rho D_1 \nabla \omega_1 + \rho \omega_1 D_1 \frac{\nabla M_n}{M_n})) = 0$$

The density of solution [2,3] and the mutual diffusion coefficients[4], were both interpolated as cubic functions of methanol concentration built into the COMSOL software package. Additionally, the average mass was taken as the molecular weight, M_n.

In the simulation of these phenomena, we used a "fine" mesh and ran the model to determine the concentration profile of the mixture at 1, 5, 10, 25, 40, 100, 250, 500, and 1200 seconds. The solutions were considered to be "completely mixed" at 1200 seconds after the onset of mixing.

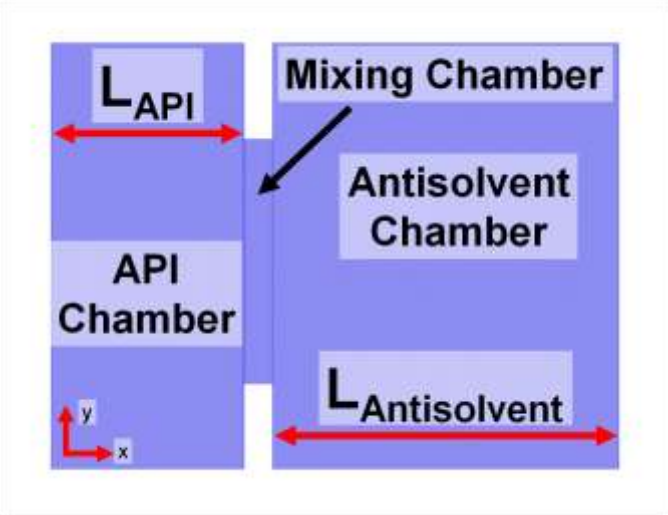

Figure S3. Schematic illustration of a well as it was modeled.

1. K. G. Mooney, M. A. Mintun, K. J. Himmelstein, *et al.*, *Journal of Pharmaceutical Sciences*, 1981, **70**, 13-22.
2. N. A. Lange and J. A. Dean, *Lange's Handbook of chemistry*, McGraw-Hill, 1979.
3. D. R. Lide, *CRC handbook of chemistry and physics: a ready-reference book of chemical and physical data*, CRC Press, 2005.
4. Z. J. Derlacki, A. J. Easteal, A. V. J. Edge, *et al.*, *The Journal of Physical Chemistry*, 1985, **89**, 5318-5322.