Microchip cocrystallization with supercritical CO_2

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Improvements in crystal engineering led to the discovery of cocrystals which benefits pharmaceutical industry. In this field, a cocrystal is a solid composed of two entities, the active pharmaceutical ingredient (API) and the coformer. Incorporation of the coformer in API modifies its crystalline phase structure and enhances its physicochemical properties, such as solubility and bioavailability [1] without altering therapeutic effects.

With the rising demand on the use of green technologies, cocrystal manufacturing strategy has recently been coupled with the use of supercritical CO_2 ($scCO_2$). The solubility of the system API+coformer is reduced in the initial solvent using supercritical CO_2 as an anti-solvent, thereby allowing precipitation [2]. Two types of $scCO_2$ precipitation techniques are described hereafter. The Gaseous Anti-Solvent (GAS) method consists in adding gradually $scCO_2$ into the solution {solvent+API+coformer} whereas in the Supercritical Anti-Solvent (SAS) method, the solution is injected into a continuous flow of $scCO_2$.

However, these techniques do not enable observations of time-related events and direct control of the crystal phase during the precipitation process. Oppositely, microfluidic platforms have been proved to be great tools for cocrystal investigations thanks to their fast screening capability, high reproducibility, precise control on hydrodynamics [3], improved heat and mass transfers and *in-situ* on-chip analysis under high pressure. Crystallization kinetics have already been studied for some organic molecules with droplet-based microfluidics [4] but not with supercritical fluid.

This presentation will first focus on the interest of using microfluidic technology for cocrystal researches with supercritical CO_2. Two strategies adopted for on-chip precipitation will be detailed afterwards. Depending on the liquid-vapor equilibrium conditions, different microchip designs have been developed. In biphasic conditions, droplets of solution {solvent+API+coformer} can be generated into a flow of $scCO_2$. The design consists in a capillary introduced into the main channel of the microchip (Figure 1a [5]).

On the other hand, in monophasic conditions, a well-based design (Figure 1b) enables to immobilize solution into wells and let CO_2 enter by diffusion. This can lead to have a composition gradient inside the well with eventually precipitation. A temperature gradient is implemented. Each well of the microchip will act as a unique microreactor allowing a fast temperature screening.

In conclusion, combination of both chip designs could give us information on composition, diffusion, precipitation and induction time by using *in-situ* analysis technologies.

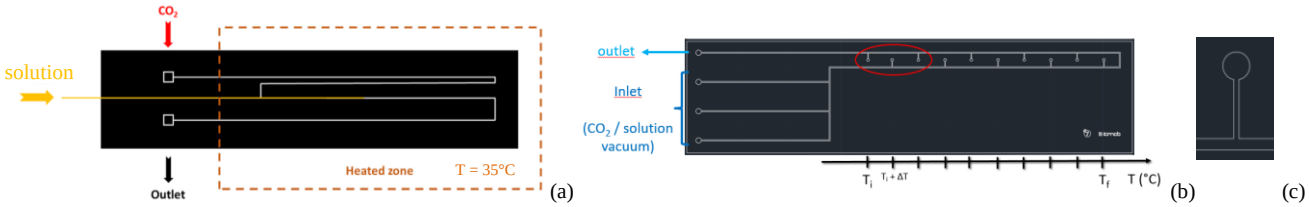

Figure 1: A capillary design for droplet generation (a), a well-based design (b) of Silicium-Pyrex microchips and a zoom on a well (c)

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