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On-chip in-situ observations of crystallization events under supercritical CO$_2$

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1. Introduction

Crystallization represents a key unit operation in separation and purification processes in the pharmaceutical industry, about 90% of active pharmaceutical ingredients (API) are obtained by this technique. Most of the API are chiral and poorly soluble in water and therefore have a low bioavailability. Understanding crystallization process can help to obtain products with desired properties. The challenge for industries is to be able to produce directly highly water soluble enantiopure drugs without going through several purification steps, which are costly, solvent and time consuming.

With the rising demand on the use of green technologies, drug manufacturing strategy has been coupled with supercritical fluids. Supercritical CO$_2$ is frequently used as an anti-solvent in batch mode, like the Gaseous Anti-Solvent (GAS) method, for recrystallization or co-crystallization$^1$.

However, such techniques do not enable observations of time-related events (kinetics, diffusion, induction time) and direct control of the crystal phase during precipitation processes. As a solution, microfluidic platforms have been proved to be a great tool for crystallization investigations thanks to their optical access for in-situ observations.

2. Materials and Methods

In this case study, the API is naproxen (NPX). Naproxen is commonly marketed in its racemic and S-enantiopure form. Their precipitation in acetone by addition of antisolvent was studied at several concentrations using microfluidic platforms, in order to have information about time-related events for enantioseparation in supercritical conditions.

High pressure microfluidic reactor was first designed then built out of Silicon-Pyrex in a clean room. The design is composed of several « pools » or « wells » with a diameter of 0.5 mm chemically etched in silicon connected by a central canal (Figure 1).

The microfluidic device is placed and heated under the optical Leica microscope. The solution [NPX+solvent] is introduced into wells. Then, the excess of the solution is evacuated with a nitrogen flush from the main channel and refilled with CO$_2$. Once CO$_2$ is added, it enters the wells by diffusion, the microscope record a « well » picture each second. A movie of NPX crystal apparition and its growth is obtained.

Furthermore, the mixing of CO$_2$ and acetone by diffusion inside the chip was simulated by numerical approaches to support the experimental results.
3. Results and discussion

In the literature, the precipitation of NPX is reported at 40 mg/mL with GAS method. Thus, in this work the experiments were conducted at this concentration at 100 bar and 40 °C. Visualization of NPX crystals and their growth as well as the modelisation of the CO$_2$-acetone diffusion are shown in Figure 2.

![Figure 2](image)

**Figure 2**: (a) On-chip precipitation of RS-NPX recorded by the optical microscope and (b) modelisation of CO$_2$-acetone diffusion.

Experimentally, nucleation and growth of NPX start in the small channel connecting the main channel to the pool and end up in it. This is in correlation with the modelisation of CO$_2$-acetone diffusion: at their interface a local supersaturation is induced, the anti-solvent effect of CO$_2$ tends to precipitate NPX with a consequent growth of needle-like crystal.

In this configuration, precipitation of racemic NPX is slightly faster than the S-enantiopure, 4 min against 6.5 min respectively (Figure 3). It indicates that the solubility of S-NPX in a mixture of CO$_2$-acetone is higher than the racemic RS-NPX at this concentration; this is in accordance with results obtained with GAS precipitation. Moreover, for RS-NPX, precipitation at different level of concentration were studied. The highest is the concentration the fastest precipitation occurs. From these data, knowledge on the growth kinetics can be acquired.

![Figure 3](image)

**Figure 3**: Induction time of racemic and S-enantiopure naproxen at 100 bar and 40°C.

In-situ chemical mapping with RAMAN spectroscopy is in progress.

4. Conclusions

The implementation of the high pressure microfluidic platform offers in-situ and real time observation of crystallization phenomena in supercritical conditions. Relevant information on the behavior of chiral and enantiopure compounds precipitation are given thanks to image analysis. These first results can be the object of a reflection on a possible enantioseparation in supercritical conditions.

References