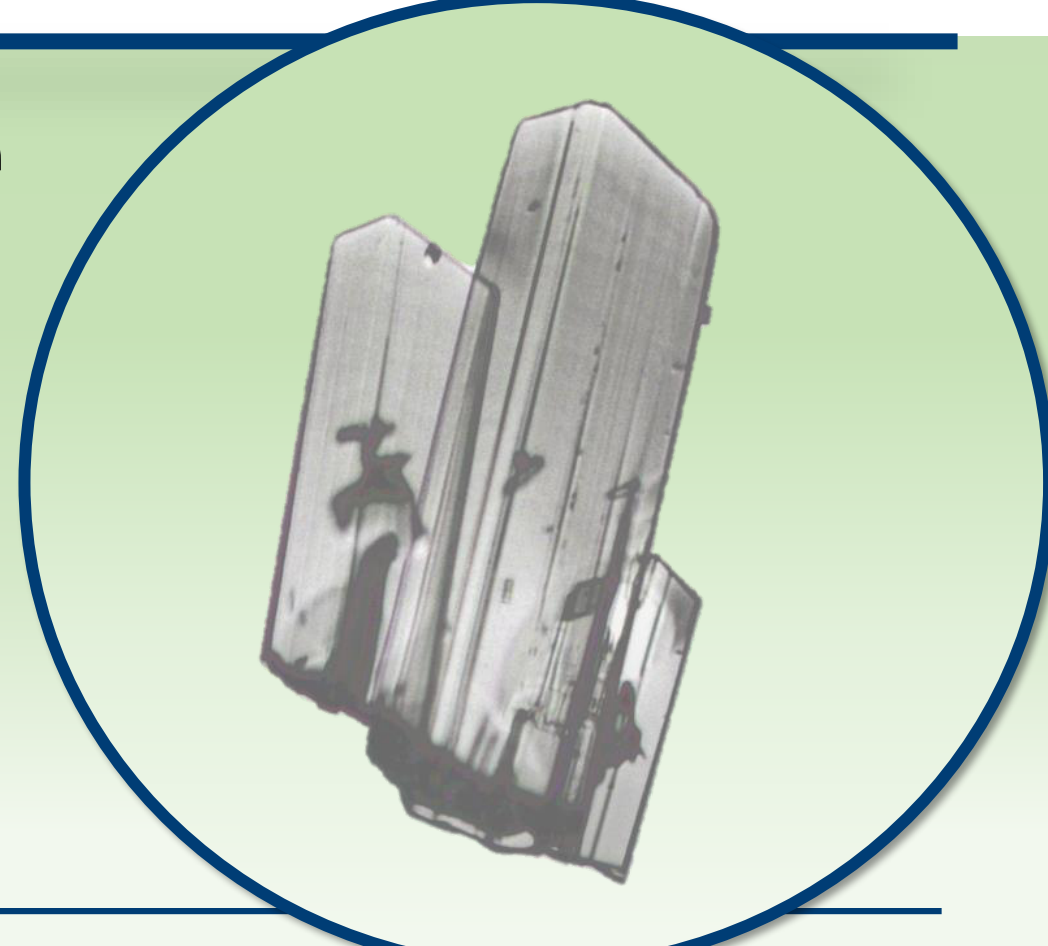


Combining synthesis and crystallization in continuous flow for the production of Ibuprofen



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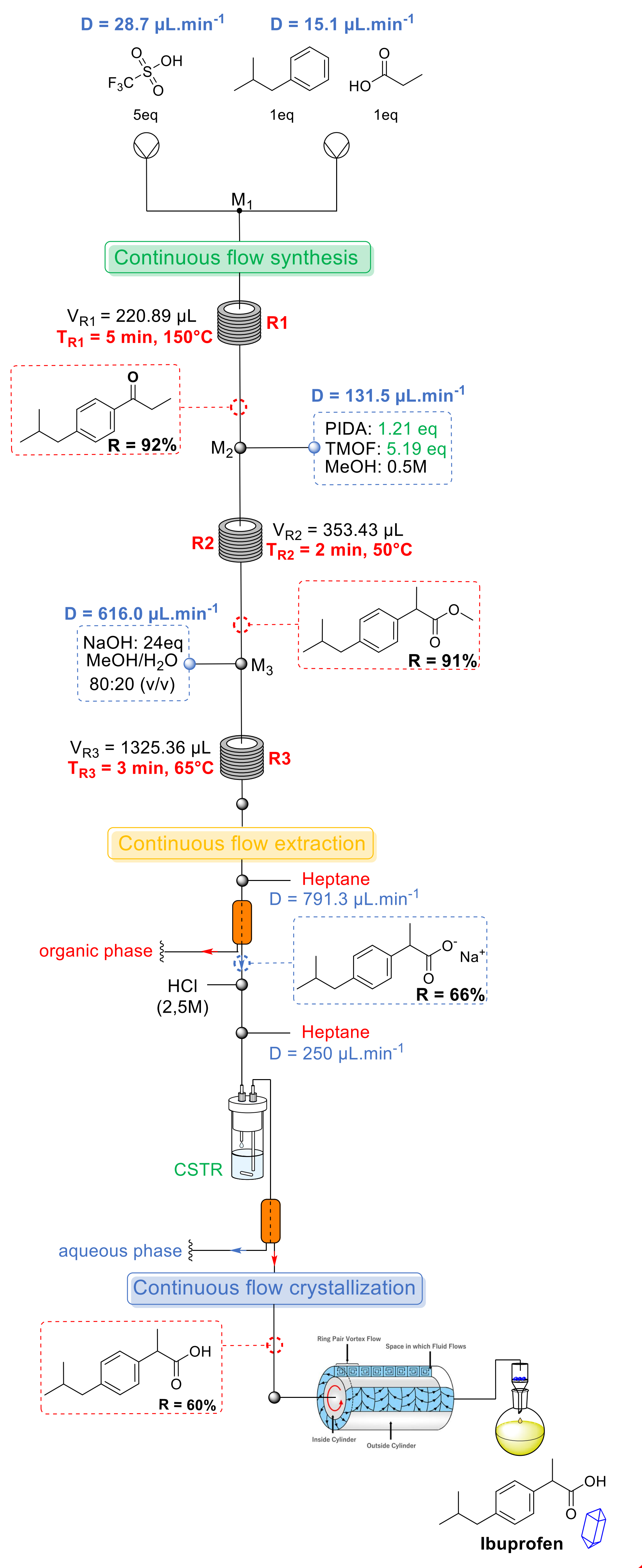
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CONTEXT

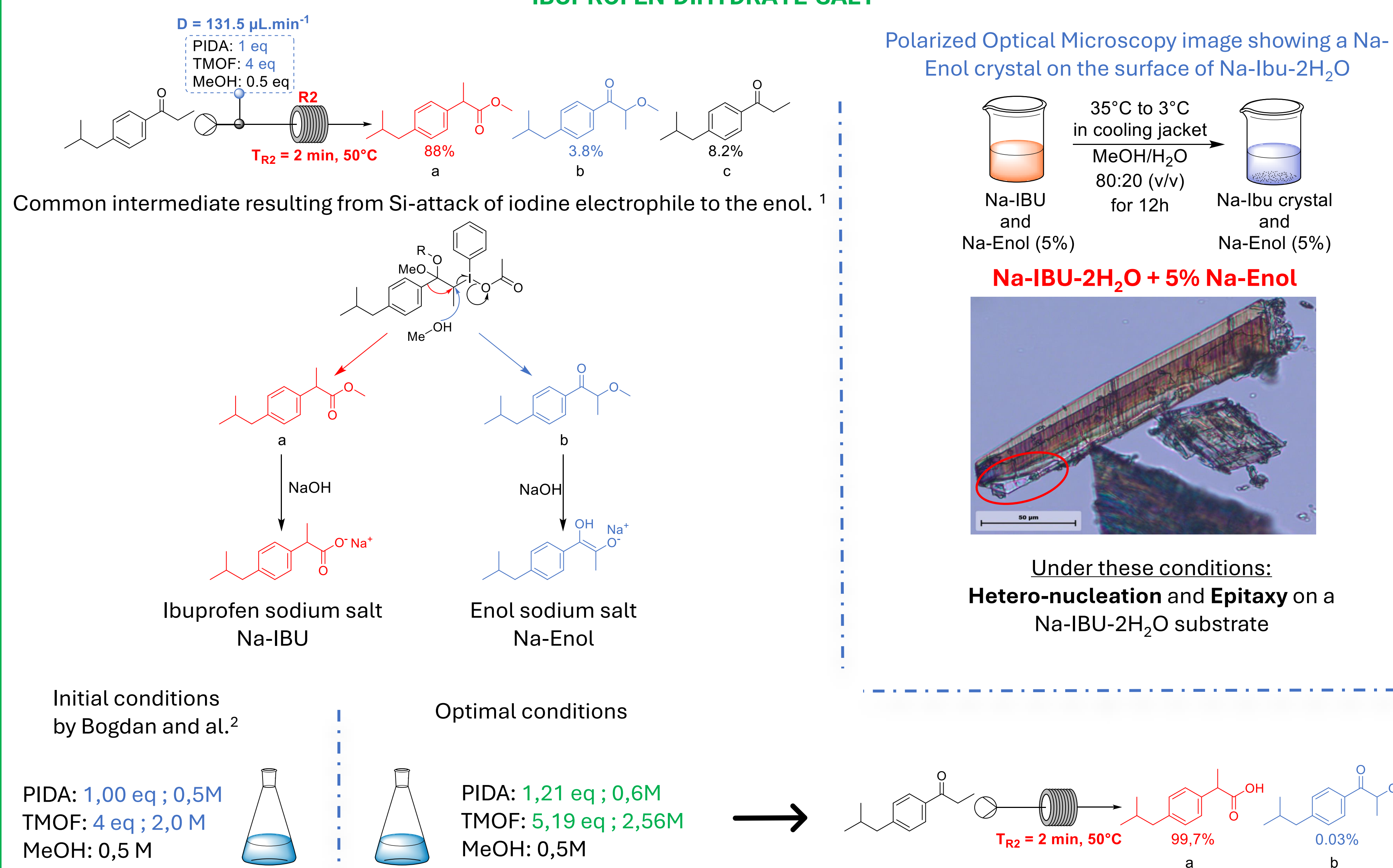
The COVID-19 crisis and the current geopolitical situation have exposed the dependence of Western countries on supplies of essential medicines (paracetamol, Ibuprofen, etc.). Industrial relocation in France and Europe is now a major strategic issue. However, the reindustrialization of fine chemicals in France, particularly for active pharmaceutical ingredients, will only be competitive with productivity gains, technological advances, and improved process safety and production methods. This project combines the expertise of continuous flow synthesis and flow crystallization in the production of active drug ingredients the Ibuprofen in the crystalline form required for their final formulation.

INNOVATION - SYNTHESIS AND CRYSTALLIZATION IN CONTINUOUS FLOW

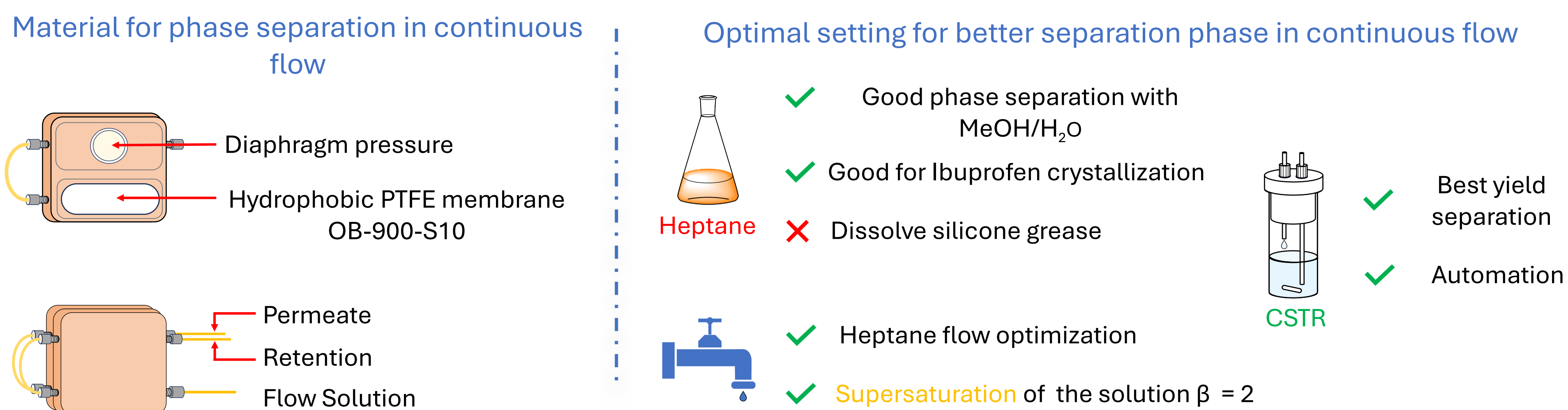
CONTINUOUS FLOW SYNTHESIS OF IBUPROFEN



FORMATION OF SODIUM ENOLATE SIDE PRODUCT DURING THE SYNTHESIS OF SODIUM IBUPROFEN DIHYDRATE SALT



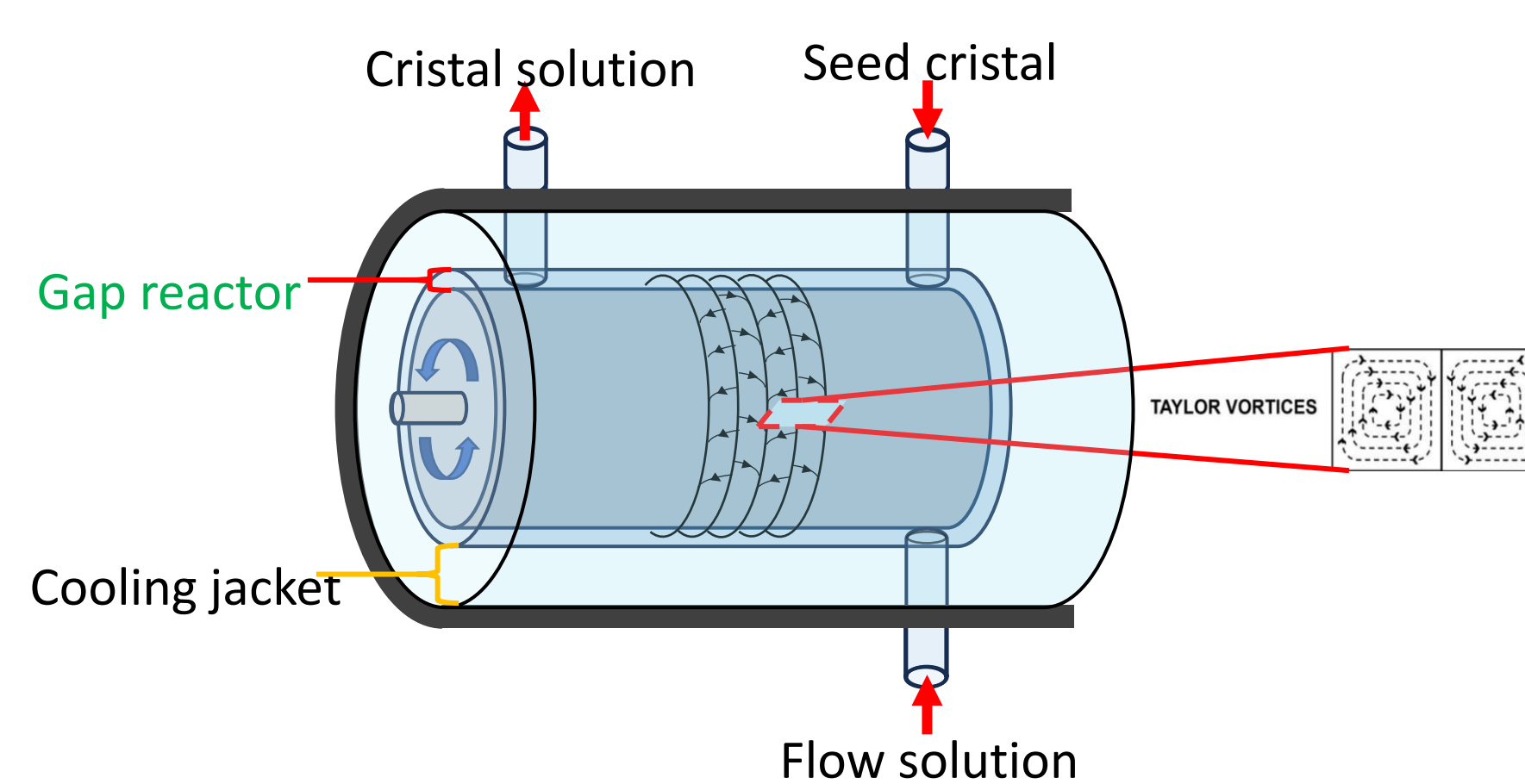
THE KEY FACTOR IN LINKING FLOW SYNTHESIS TO FLOW CRYSTALLIZATION



CONTINUOUS FLOW CRYSTALLIZATION

Couette-Taylor reactor

The reactor is composed of two co-axial cylinders with a narrow gap them.^{3,4} The fast rotation of the inner cylinder generates Taylor vortex-type flows, favoring mixing, mass transfer and high shear forces beneficial for crystallization.⁵



Optimal setting for Ibuprofen crystallization by Couette-Taylor reactor

- 5°C
- Supersaturation control
- 1000 rpm
- Control of Taylor vortex flow
- 4 ml.min⁻¹
- Residence time (tr)
- Gap: 1mm
- Control of the crystal size distribution

RESULTS

tr = 10 min
 tr = 7 min 30s
788.4 mg.h⁻¹ Ibuprofen
 Combining continuous flow synthesis and continuous crystallization
 Ibuprofen crystallization in Couette-Taylor reactor

CONCLUSION

A complete continuous-flow process for the synthesis of ibuprofen, coupled with a continuous crystallization has been achieved. After optimizing the key parameters of each essential stage synthesis part, work-up processing, and crystallization. We successfully obtained racemic ibuprofen dihydrate in crystalline form under continuous-flow conditions, with a productivity of 788 mg.h⁻¹. This compact, scalable process offers major gains in surface area, quality and cost, positioning this project as a strategic solution for the European pharmaceutical industry.

ACKNOWLEDGMENTS

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