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## Continuous chiral resolution by diastereomeric salt formation of racemic Ibuprofen in a Couette-Taylor crystallizer

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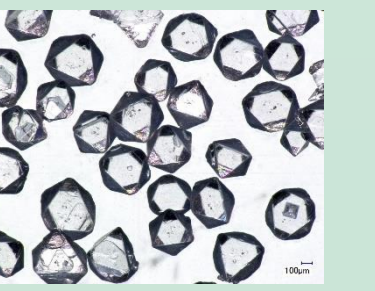
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## Introduction

### Batch production mode [1]

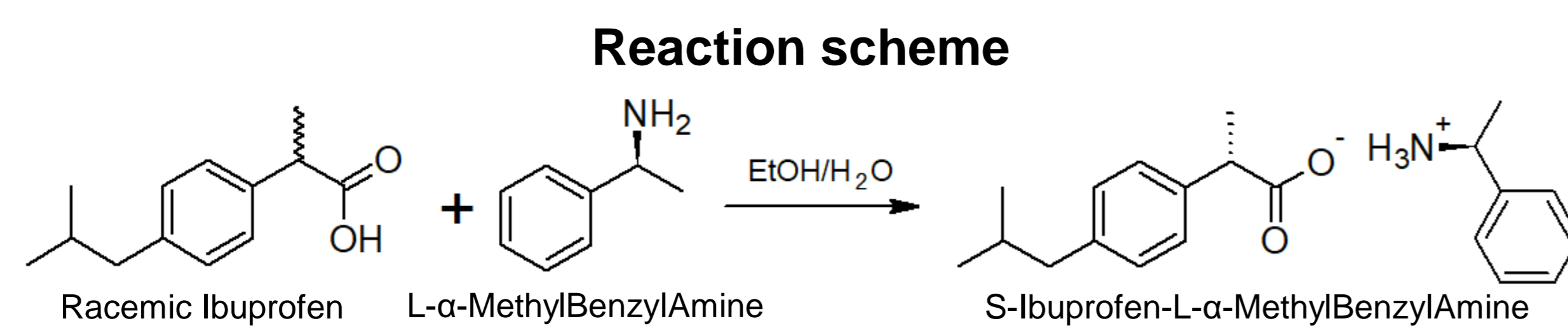
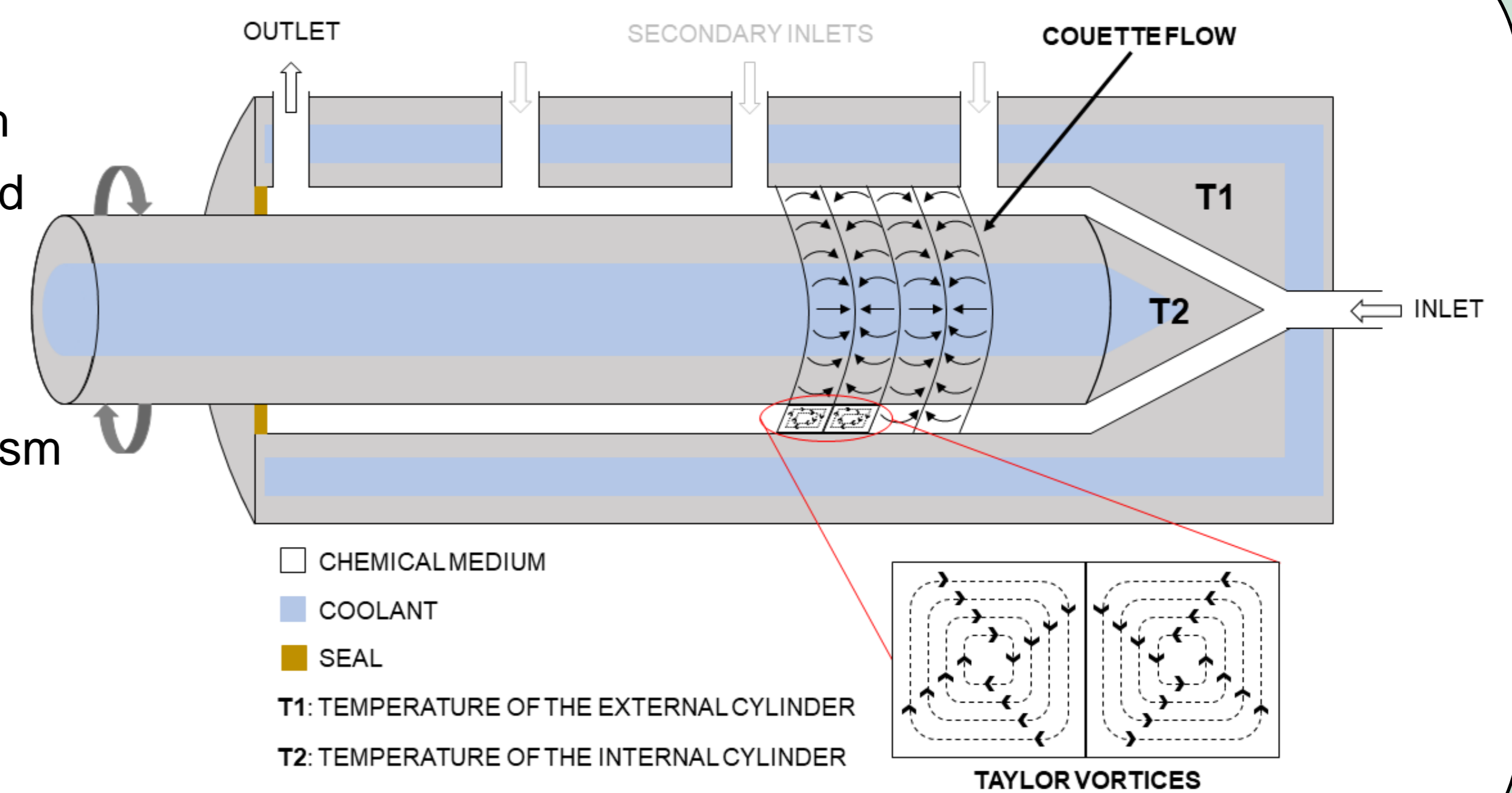
- legacy in pharmaceutical industry
- weaknesses such as batch-to-batch quality variation

### Continuous production mode [2]

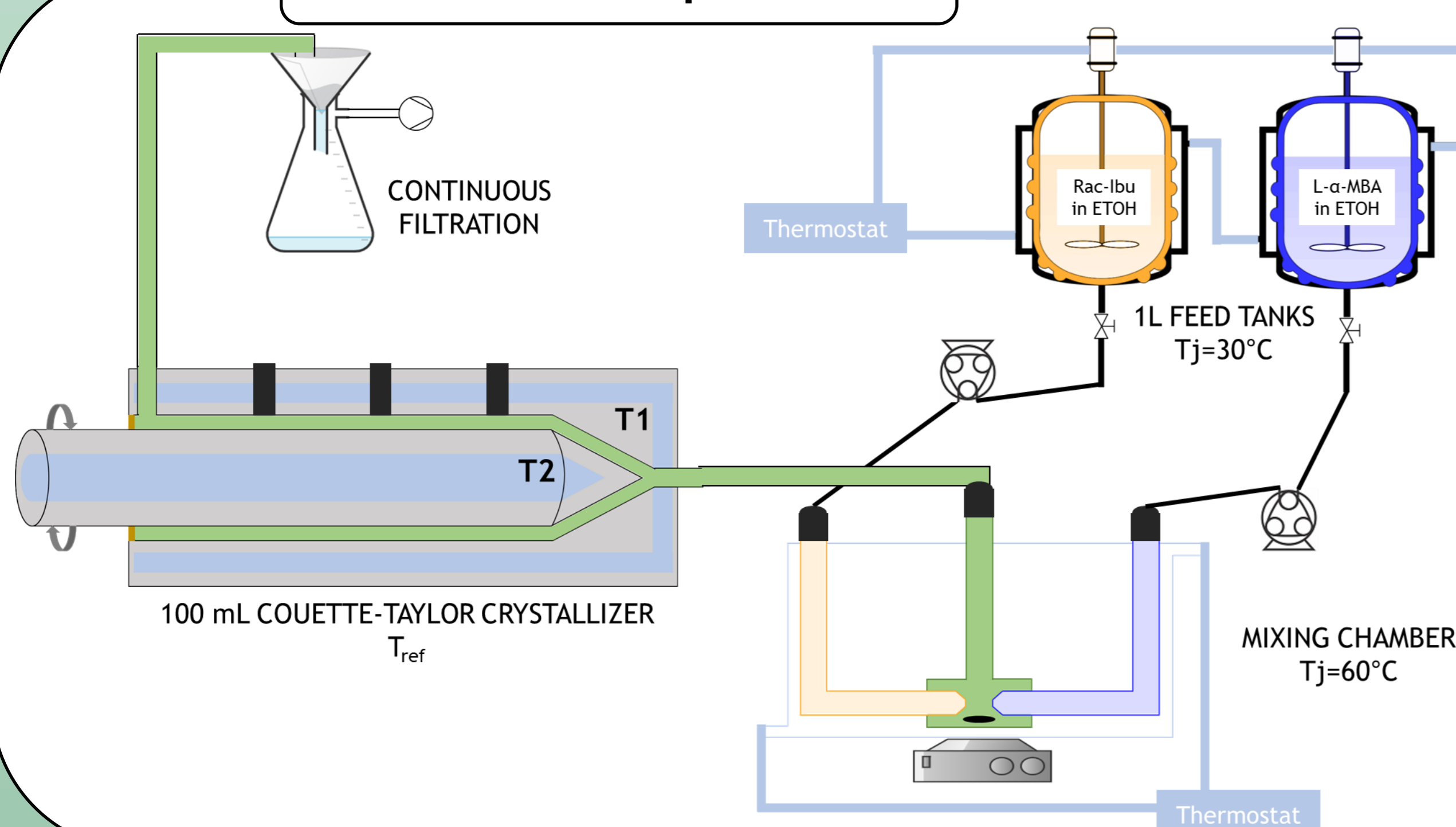
- steady-state functioning, i.e., more constant quality product
- better process control

### Couette-Taylor crystallizer

- specific flow characteristics at high rotation speed: Couette flow coupled with Taylor vortices [3]
- impact on crystal size distribution (CSD), morphology and polymorphism in crystallization processes [4]



## Continuous process



### 7 parameters to investigate

- (1) Absolute temperature difference  $|\Delta T|$
- (2) Sign of  $\Delta T$
- (3) Stirring speed  $\Omega$
- (4) Residence time  $t$  (i.e., flowrate)
- (5) Temperature inside the CT crystallizer ("central point" of the two coolant set temperatures)  $T_{ref}$
- (6) Medium dilution
- (7) EtOH/H<sub>2</sub>O mass ratio

### Rationalized study through a Design of Experiments (DoE)

#### First screening with 4 factors

- (1)(2) Temperature difference  $\Delta T$
  - (3) Stirring speed  $\Omega$
  - (4) Residence time  $t$  (i.e., flowrate)
  - (5) Temperature inside the CT crystallizer ("central point" of the two cryostat set temperatures)  $T_{ref}$
- Fixed medium dilution (15V) and EtOH/H<sub>2</sub>O mass ratio (80/20)

## Design of Experiments

Factor	Levels		
$\Delta T$ (°C)	-10 (T <sub>1</sub> >T <sub>2</sub> )	0 (T <sub>1</sub> =T <sub>2</sub> )	+10 (T <sub>1</sub> <T <sub>2</sub> )
$\Omega$ (rpm)	200	500	1000
$t$ (min)	5	15	30
$T_{ref}$ (°C)	15	20	25

### 5 main responses to study

1. Global productivity (g/L/min)
2. Global yield (%)
3. Diastereomeric excess
4. Diastereomeric productivity (g/L/min)
5. Diastereomeric yield (%)

- **Most impacting factor(s)**
- **Best factor level**

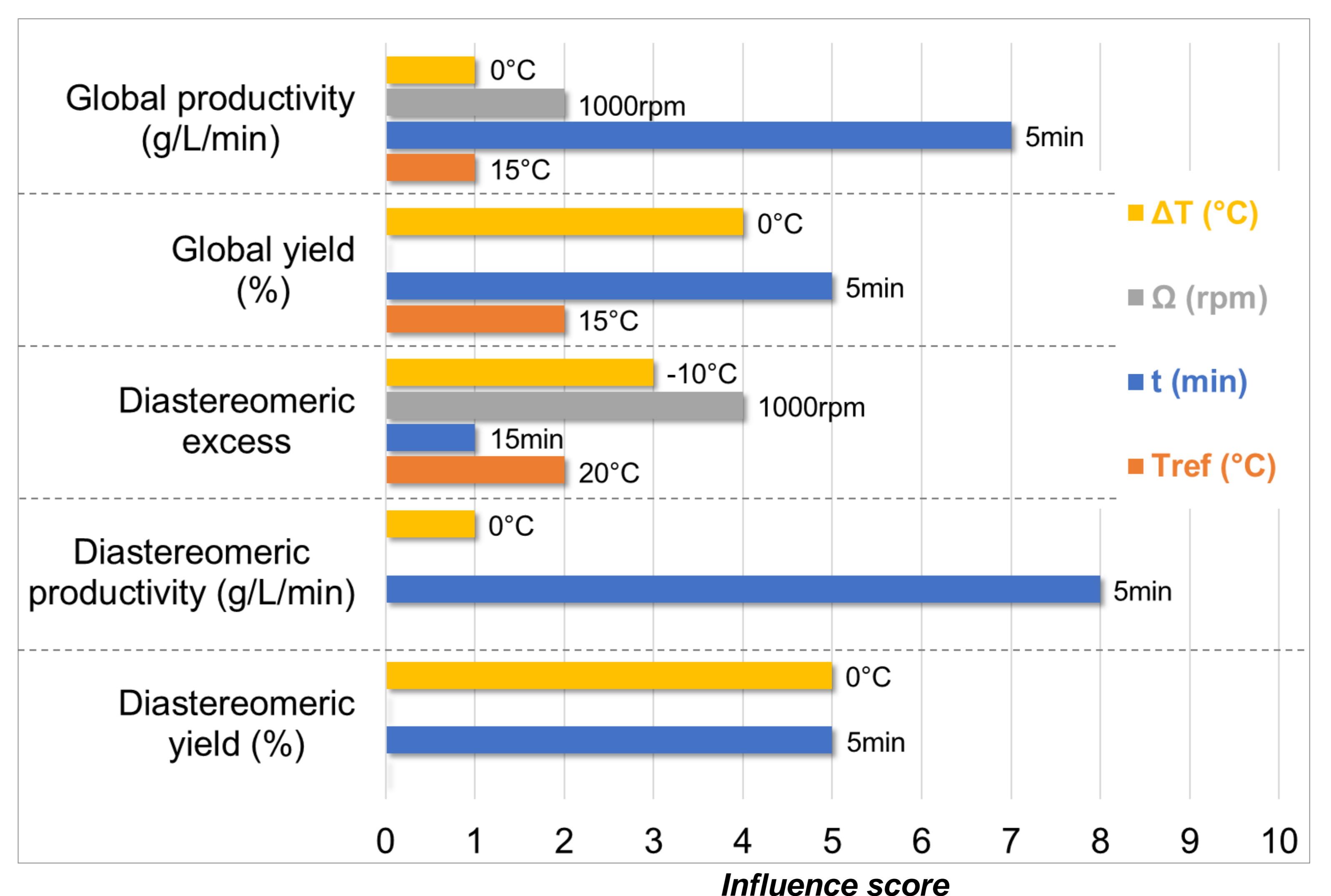
## Conclusions and perspectives

- ⇒ Thanks to the set up of a **Design of Experiments**, trends were identified on the 4 studied factors in order to **favor yield, productivity and/or diastereomeric excess**.
- ⇒ With the **suitable parameter set**, the **chiral purity** of the recovered product is **higher** than that obtained in **batch mode**.
- ⇒ The **yield** is generally **lower** than that obtained in batch mode. However, experiments performed on a period exceeding **10 residence times** suggest that it **improves after 14 resident times**. **Changes** should be done on the **current set-up** in order to confirm this trend.
- ⇒ **Further work** should be done on specific ranges determined by this first screening, in order to draw a **response surface** for the **7 parameters** to be studied.
- ⇒ **Potential interaction(s)** between factors should also be examined, as it has already been seen that the **combination of both  $\Omega$  and  $\Delta T$**  can have an influence on chiral purity and crystal size [5].

## Results

From 16 experiments (including 4 repeated ones) lasting 10 residence times:

### Relative influence of each studied factor on the main responses and best factor level for influence score $\geq 1$



Temperature difference $\Delta T$ (°C)	Stirring speed $\Omega$ (rpm)	Residence time $t$ (min)	Cryostat average set temperature $T_{ref}$ (°C)
⇒ $\Delta T > 0$ seems to enhance chiral purity	⇒ 1000rpm seems to be the best factor level	⇒ Favor lower residence times	⇒ Apparent poor influence
⇒ Avoid T <sub>1</sub> <T <sub>2</sub>	⇒ 200 and 500rpm eliminated	⇒ Avoid 30min	⇒ Favor lower temperatures

### [References]

- [1] Y. Ma et al., Organic process Research & Development, vol. 24, n°10, p. 1785-1801 (2020).
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- [3] W.-S. Kim, Journal of Chemical Engineering of Japan, vol. 47, n°2, p. 115-123 (2014).
- [4] W.-S. Kim, T. Yu, Z. Wu, U.S. Patent Application 2017/0081188 A1 (2017)
- [5] M. Schindler, Thèse de doctorat : physique. Rouen: Université de Rouen Normandie, 2020, 144p.