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

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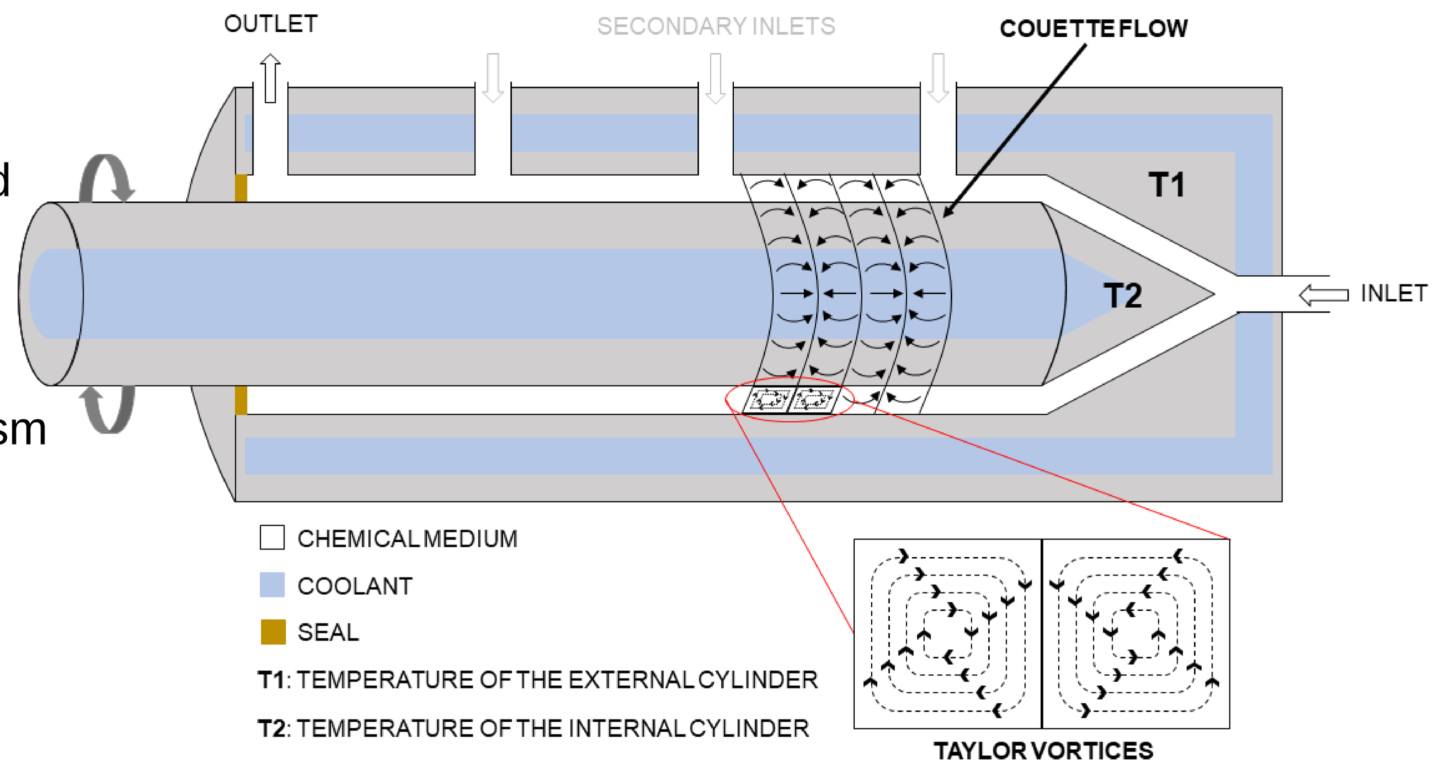
Introduction

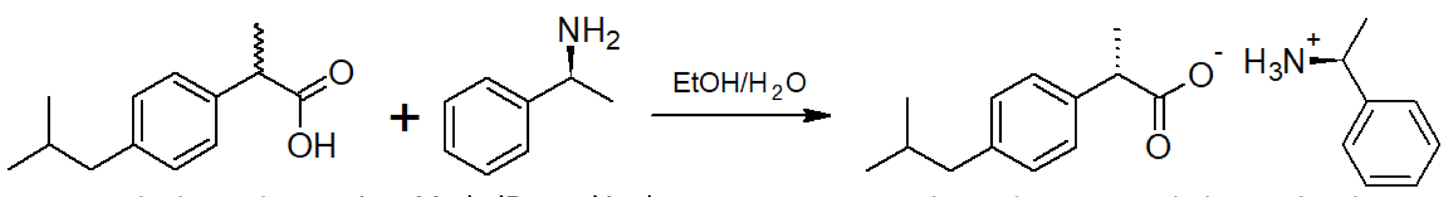
Batch production mode [1]
- legacy in pharmaceutical industry
- weaknesses such as batch-to-batch quality variation

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]

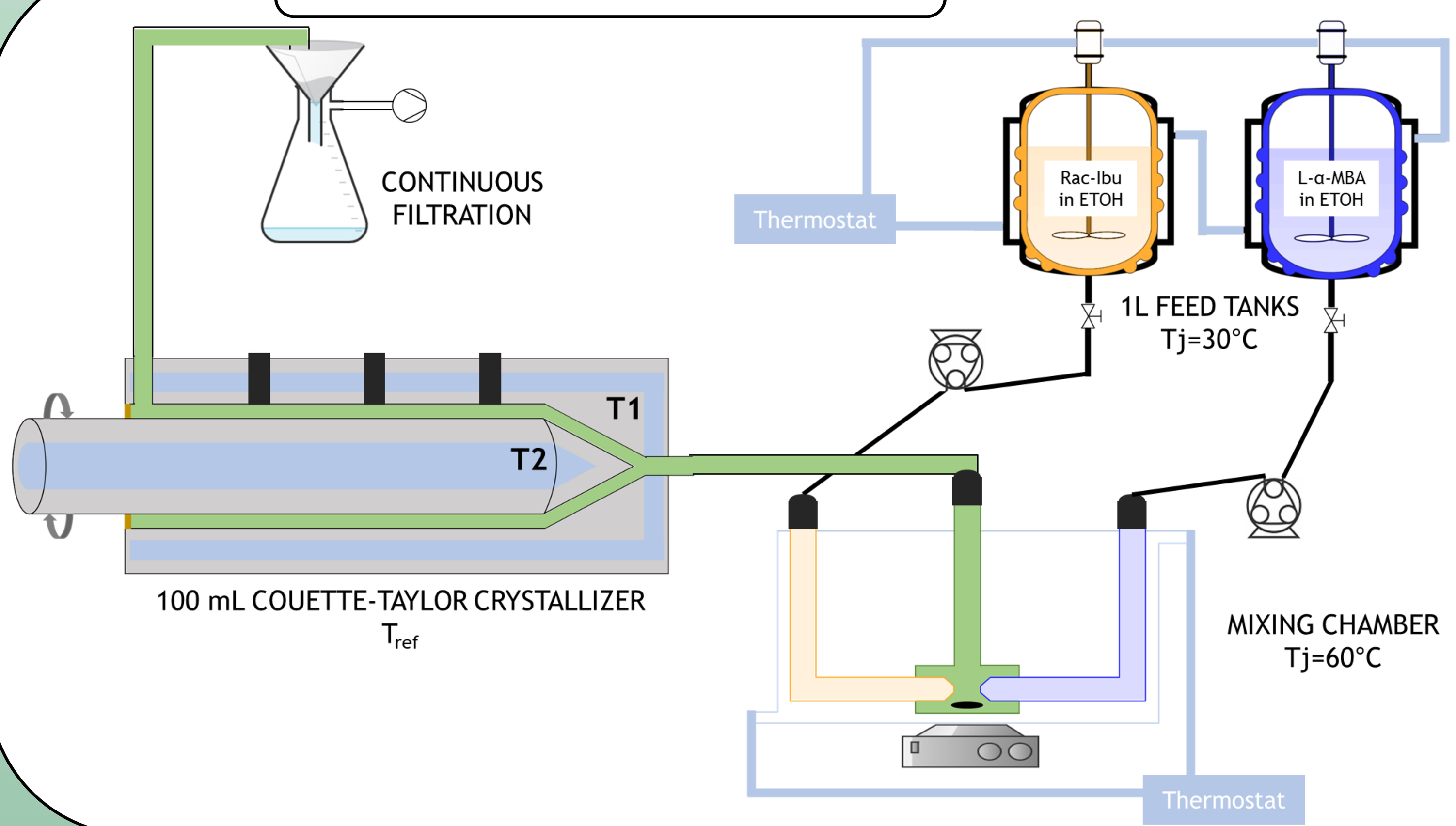


Reaction scheme



Racemic Ibuprofen + L-α-MethylBenzylAmine → S-Ibuprofen-L-α-MethylBenzylAmine

Continuous process



7 parameters to investigate
(1) Absolute temperature difference |ΔT|
(2) Sign of ΔT
(3) Stirring speed Ω
(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_2O mass ratio

⇒ **Rationalized study through a Design of Experiments (DoE)**

First screening with 4 factors
(1)(2) Temperature difference ΔT
(3) Stirring speed Ω
(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/H2O mass ratio (80/20)

Design of Experiments

Factor	Levels		
ΔT (°C)	-10 (T1>T2)	0 (T1=T2)	+10 (T1<T2)
Ω (rpm)	200	500	1000
t (min)	5	15	30
T_{ref} (°C)	15	20	25

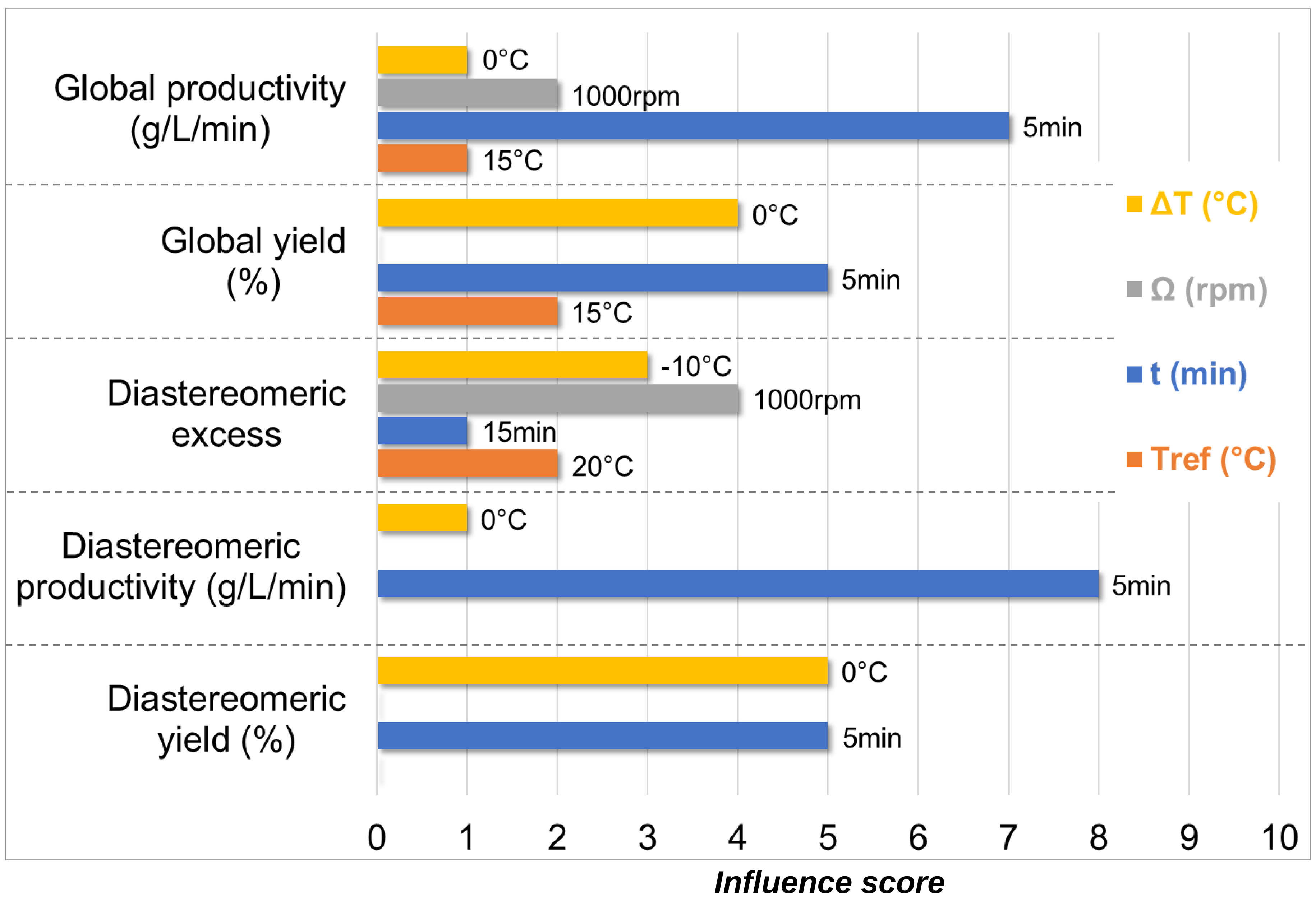
5 main responses to study
1. Global productivity (g/L/min)
2. Global yield (%)
3. Diastereomeric excess
4. Diastereomeric productivity (g/L/min)
5. Diastereomeric yield (%)

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

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 ≥1



Temperature difference ΔT (°C)	Stirring speed Ω (rpm)	Residence time t (min)	Cryostat average set temperature T_{ref} (°C)
⇒ ΔT>0 seems to enhance chiral purity	⇒ 1000rpm seems to be the best factor level	⇒ Favor lower residence times	⇒ Apparent poor influence
⇒ Avoid T1<T2	⇒ 200 and 500rpm eliminated	⇒ Avoid 30min	⇒ Favor lower temperatures

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 Ω and ΔT** can have an influence on chiral purity and crystal size [5].

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