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

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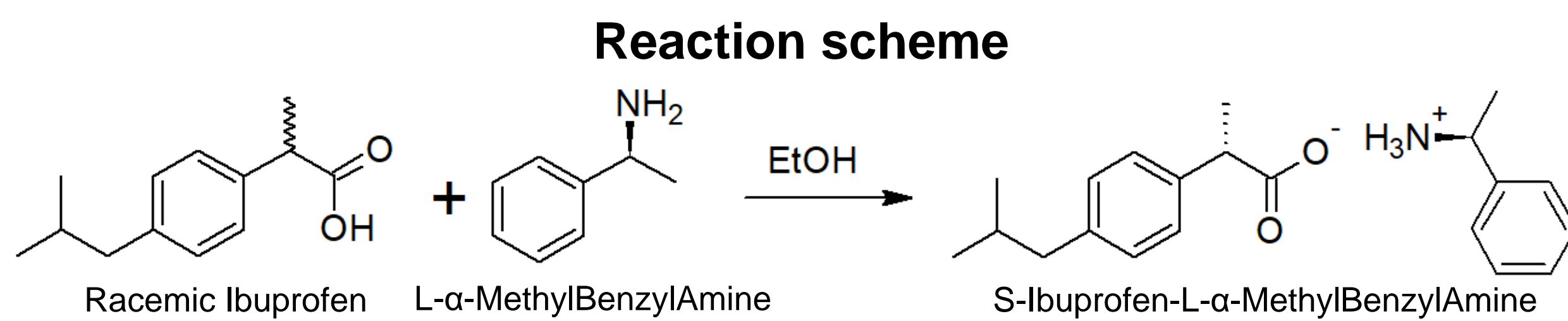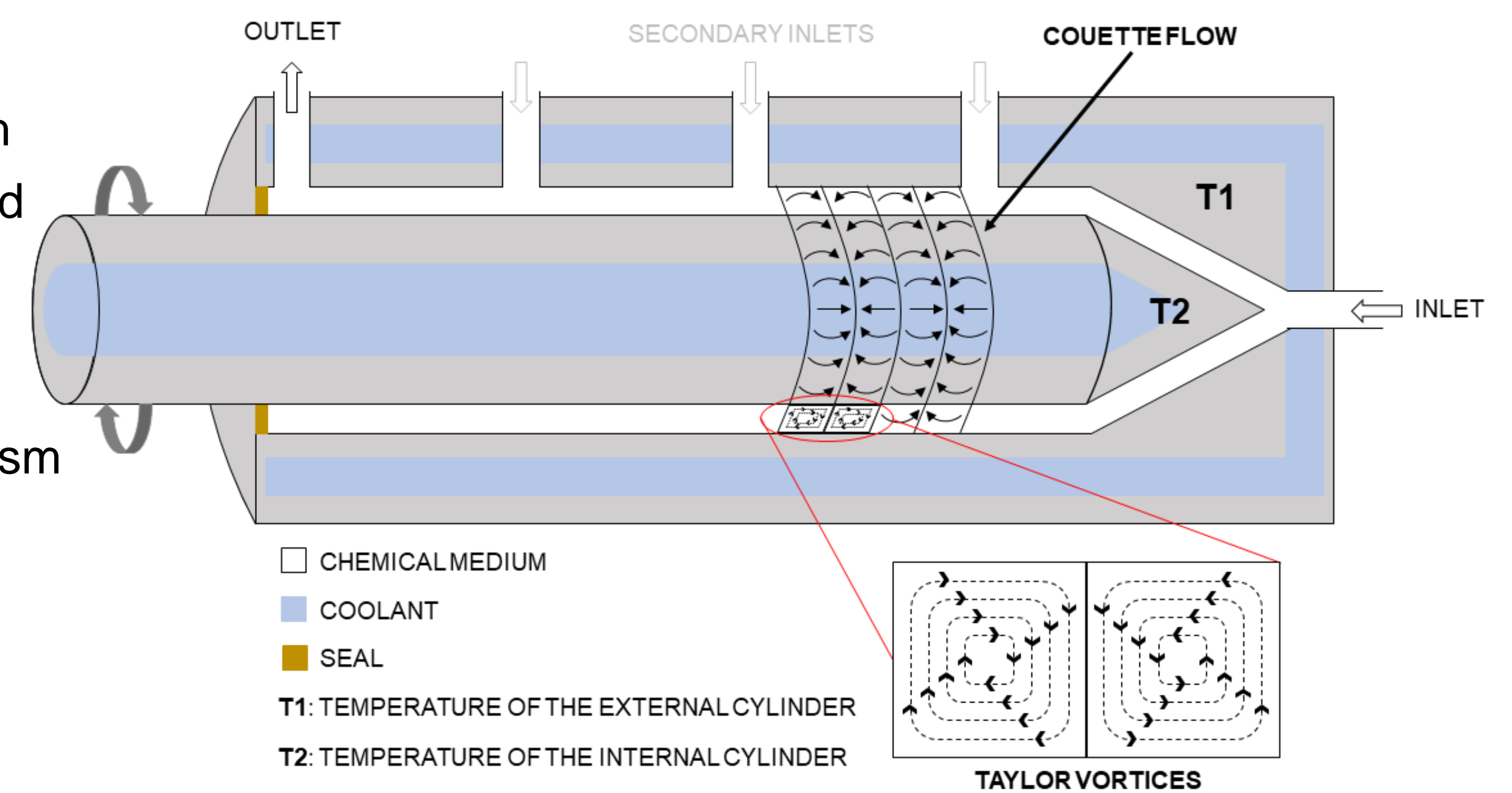
Introduction

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]

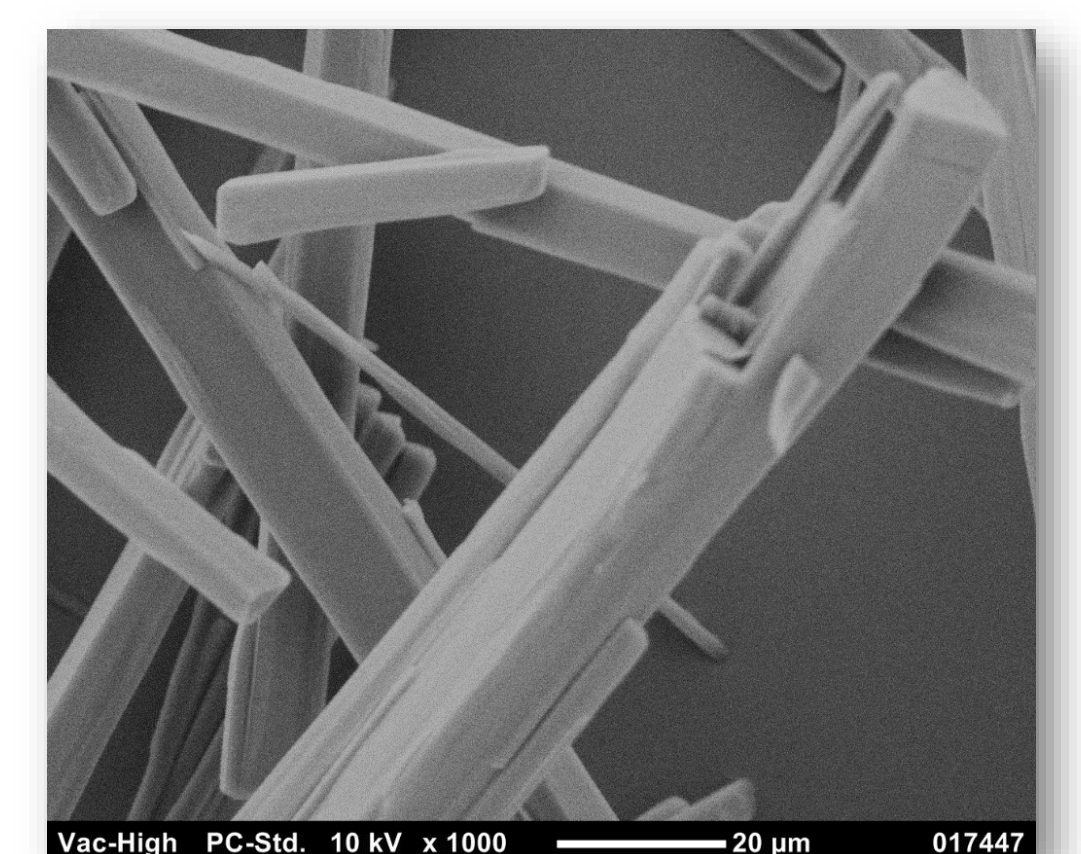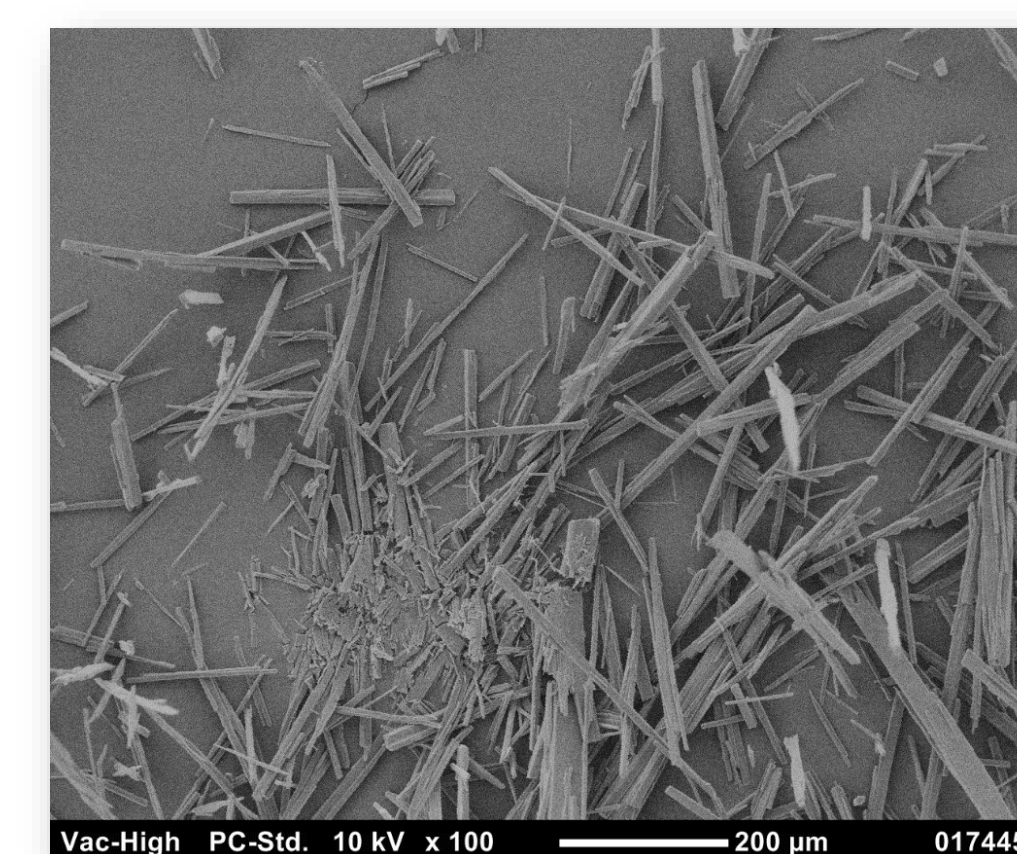- impact on crystal size distribution (CSD), morphology and polymorphism in crystallization processes [4]
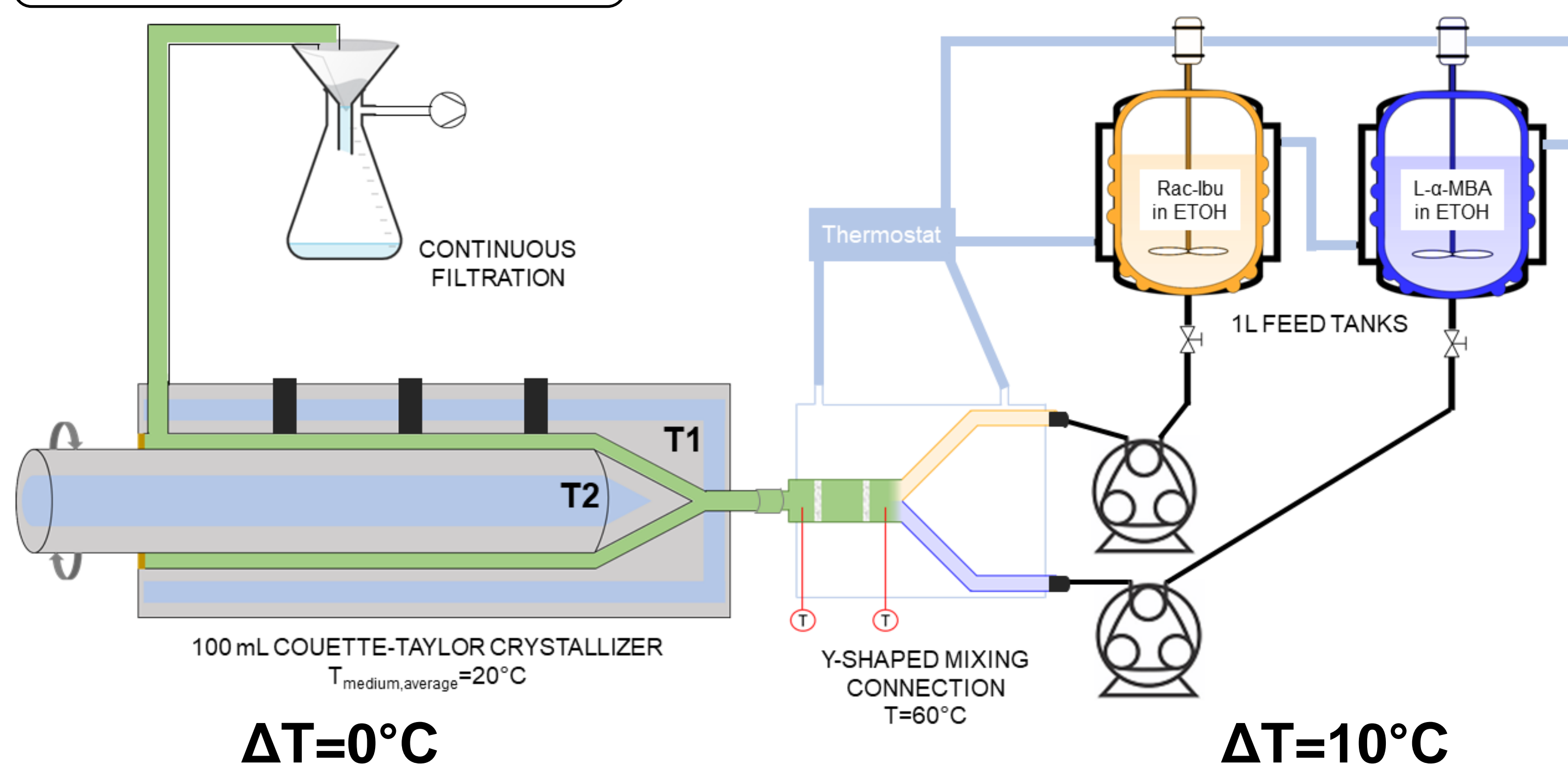
OUTLET SECONDARY INLETS COUETTE FLOW

T1

T2

INLET

☐ CHEMICAL MEDIUM
☐ COOLANT
☐ SEAL
T1: TEMPERATURE OF THE EXTERNAL CYLINDER
T2: TEMPERATURE OF THE INTERNAL CYLINDER

TAYLOR VORTICES

Reaction scheme

Racemic Ibuprofen + L-α-MethylBenzylAmine → (EtOH) → S-Ibuprofen-L-α-MethylBenzylAmine

Batch process

Conditions — Scale: 10g — Stirring speed (mechanical stirrer): 200rpm

Results

Yield	Diastereomeric excess	Diastereomeric yield
41%	0.58	24%

Vac-High PC-Std. 10 kV x 100 — 200 µm — 017445
Vac-High PC-Std. 10 kV x 1000 — 20 µm — 017447

Continuous process

CONTINUOUS FILTRATION

Thermostat

Rac-Ibu in ETOH

L-α-MBA in ETOH

1L FEED TANKS

100 mL COUETTE-TAYLOR CRYSTALLIZER T$_{medium,average}$=20°C

Y-SHAPED MIXING CONNECTION T=60°C

T1
T2

Conditions

Scale:	Stirring speed Ω:	Flowrate:
70g	1000rpm	3.34mL/min

=> Variation of the temperature difference between the two cylinders with T2>T1

ΔT=0°C

Yield and productivity ΔT=0°C

(Legend: Yield, Diastereomeric yield, Global productivity, Diastereomeric productivity)

Yield (%) / Productivity (g/min) / Fraction

Vac-High PC-Std. 10 kV x 100 — 200 µm — 017458
Vac-High PC-Std. 10 kV x 1000 — 20 µm — 017454
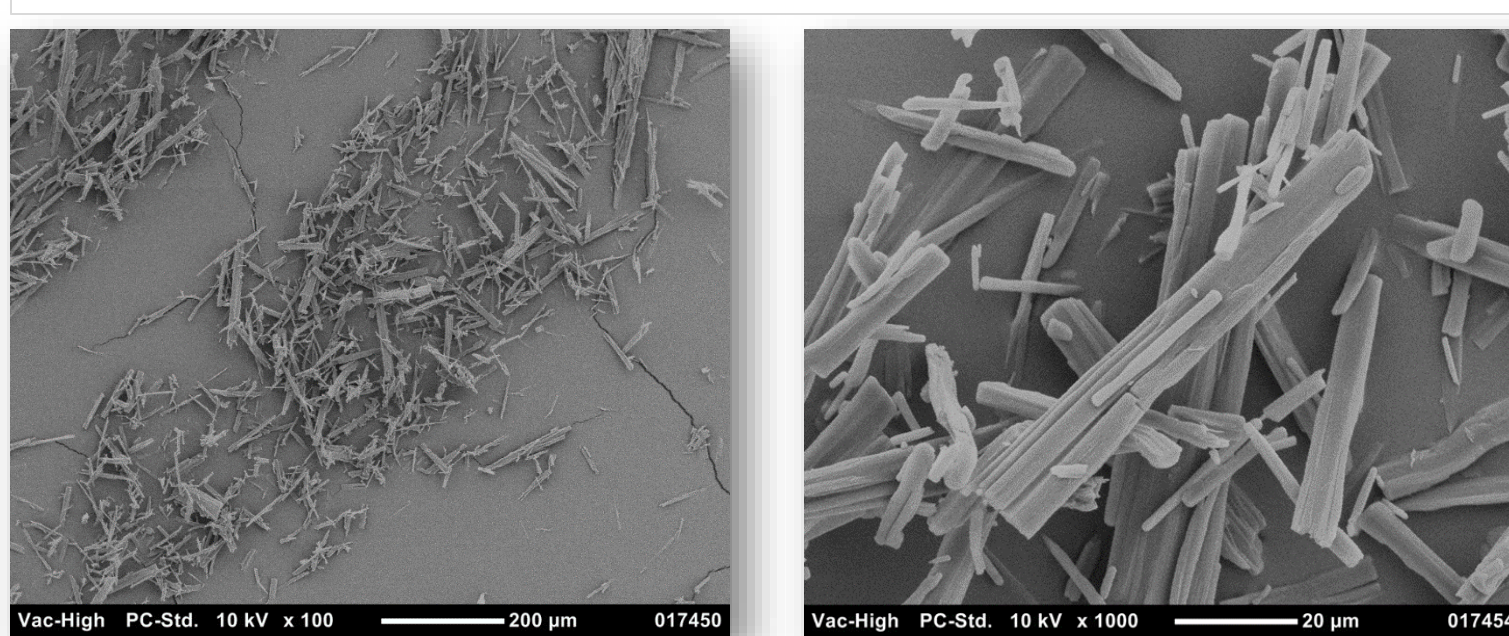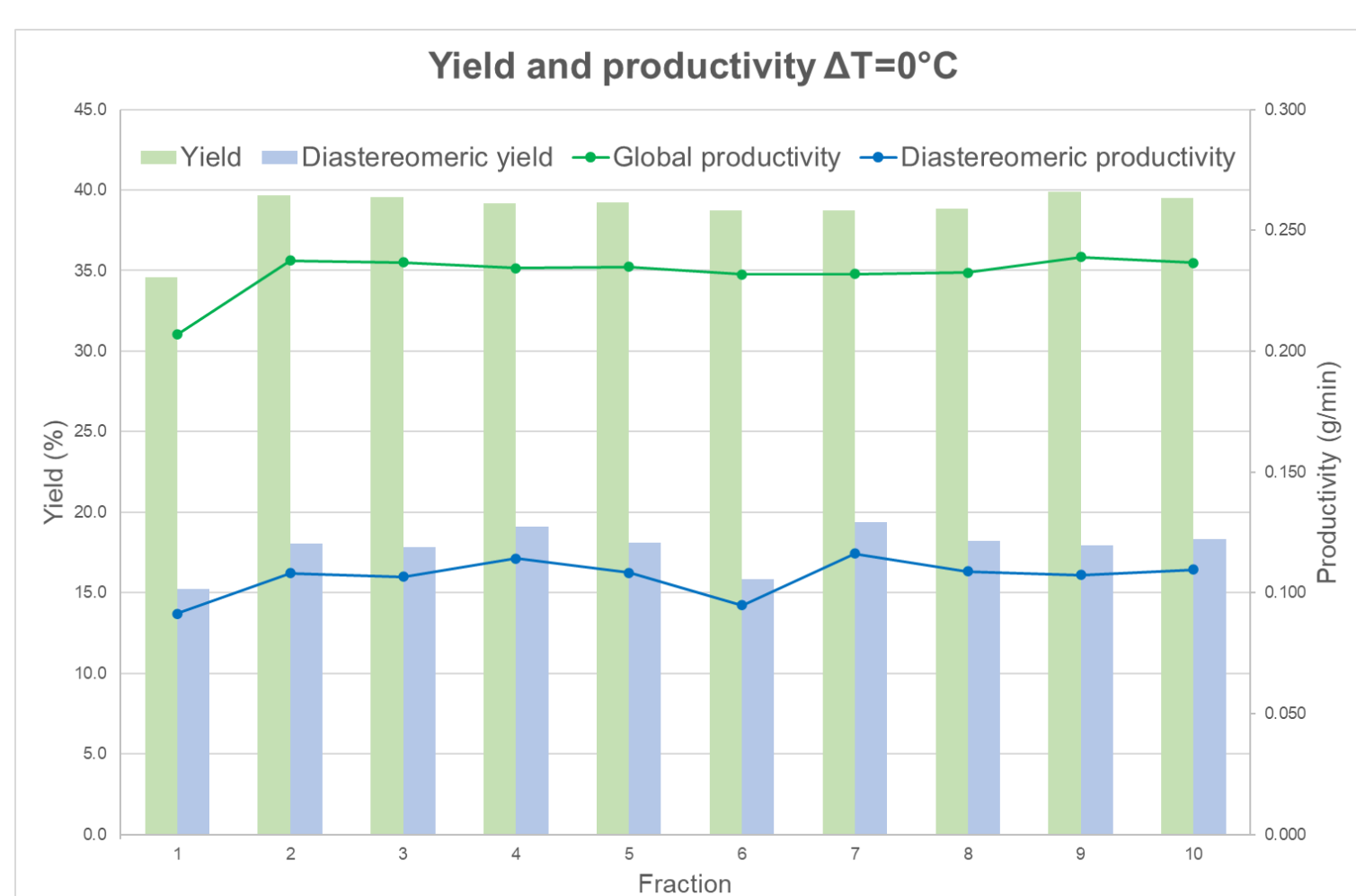
⇒ **Steady state functioning** reached quickly

ΔT=10°C

Yield and productivity ΔT=10°C

Vac-High PC-Std. 10 kV x 100 — 200 µm — 017459
Vac-High PC-Std. 10 kV x 1000 — 20 µm — 017462
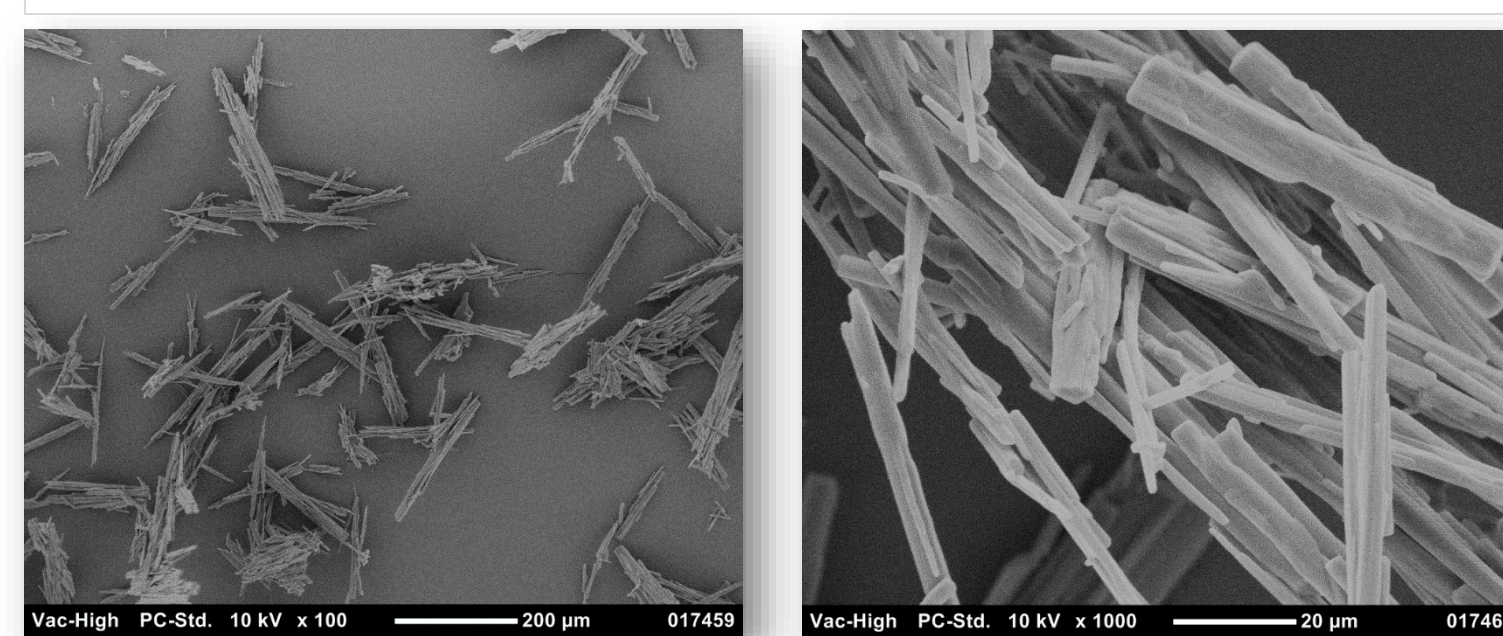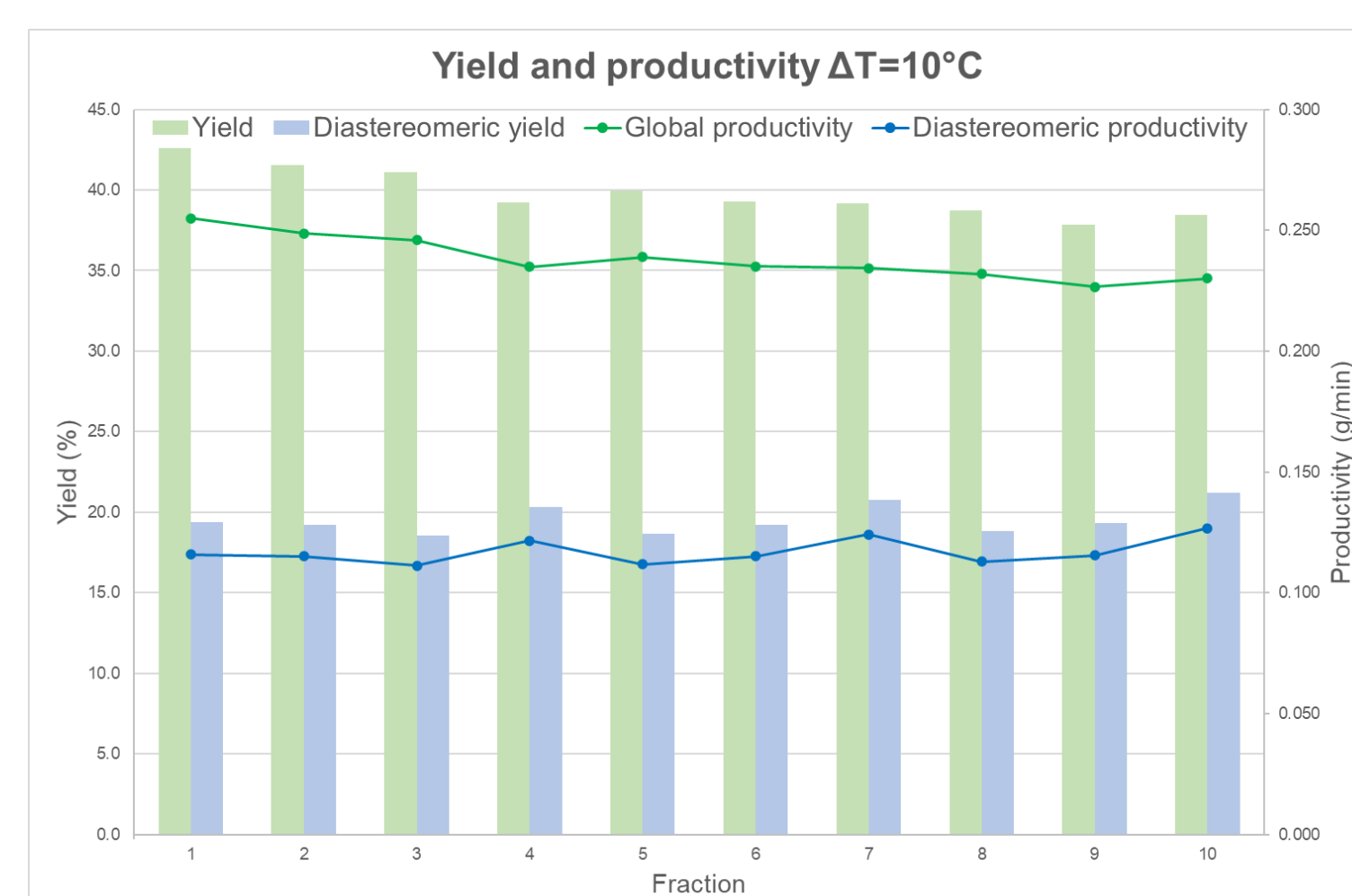
⇒ **Crystal size** increases when the temperature difference increases

ΔT=20°C

Yield and productivity ΔT=20°C

Vac-High PC-Std. 10 kV x 100 — 200 µm — 017477
Vac-High PC-Std. 10 kV x 1000 — 20 µm — 017478
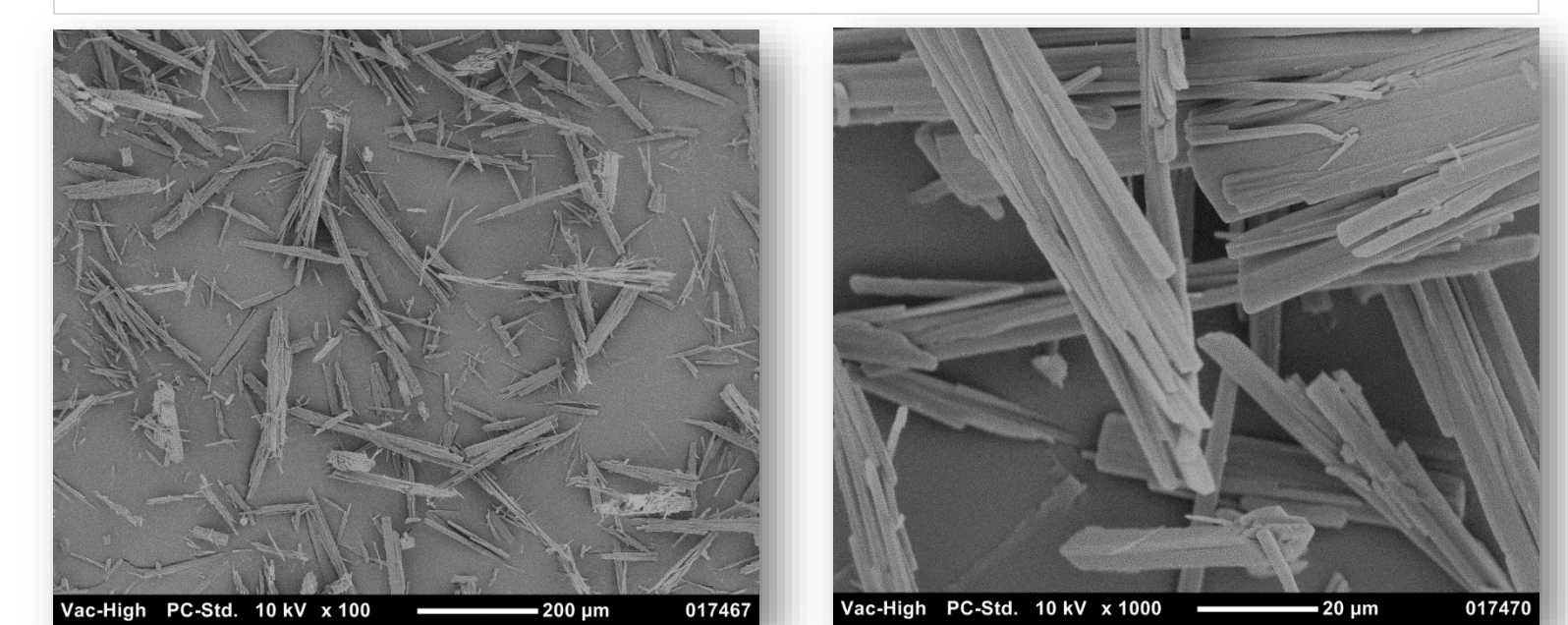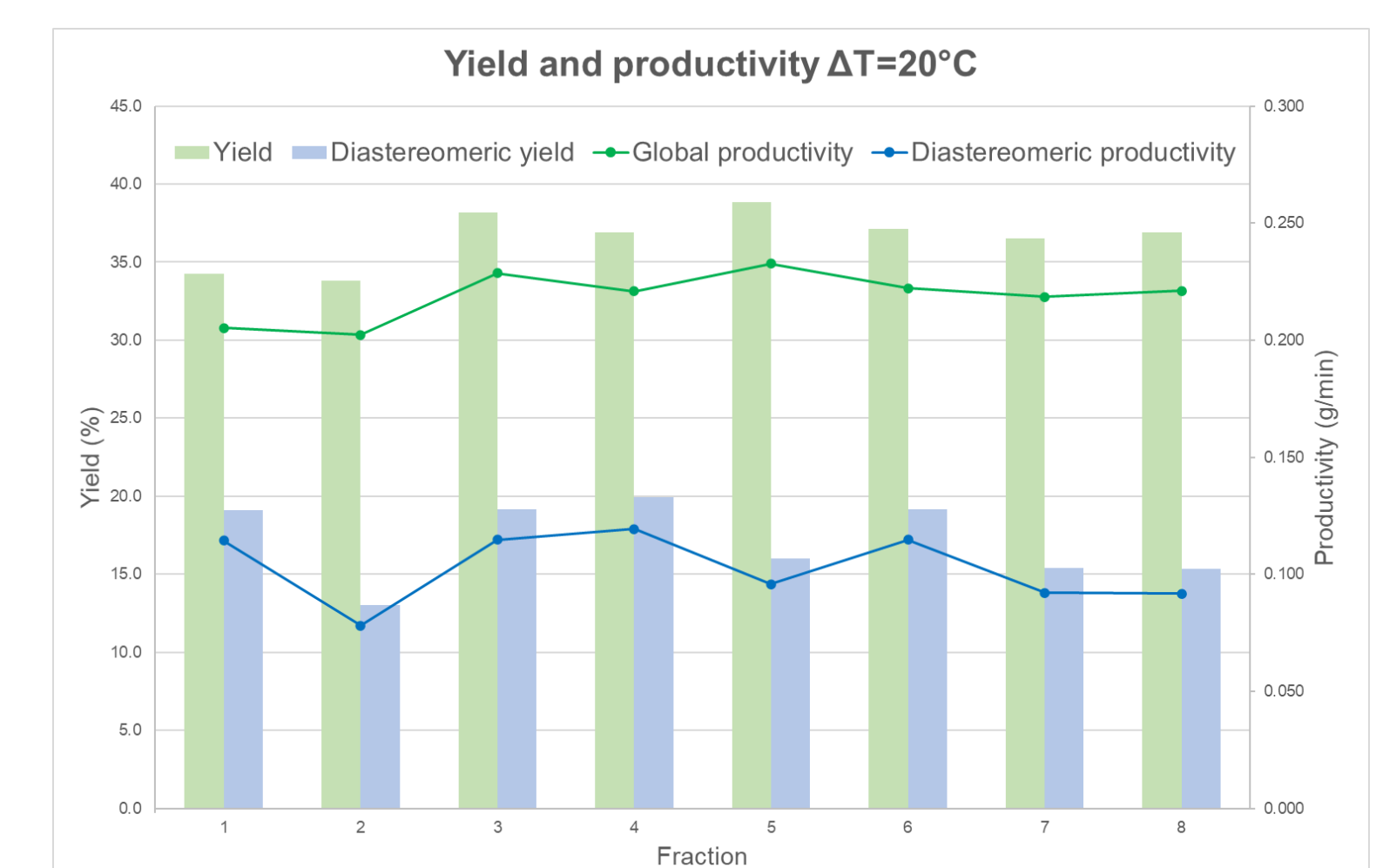
⇒ At this ΔT, the product quality variation can be due to the crystal size

⇒ **ΔT=10°C seems to give the best results regarding product quality**

Conclusions and perspectives

⇒ The **yield** of the **continuous process** is **close to that obtained in batch mode**. By contrast, the **chiral purity** is lower than that of the batch mode. The reason might be linked to the **filtration process** which is not adapted to the continuous mode.

⇒ It is noteworthy that the **combination of both Ω and ΔT** can have an influence on chiral purity and crystal size [5].

⇒ The continuous process needs to be optimized by studying **variations of the stirring speed Ω, the flowrate, the temperature inside the CT crystallizer, and the sign of ΔT.**

[References]

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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, (Mar. 23 2017)

[5] M. Schindler, Thèse de doctorat : physique. Rouen: Université de Rouen Normandie, 2020, 144p.