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Direct chiral resolution of Praziquantel through preferential crystallization of a conglomerate cocrystal

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Direct chiral resolution of Praziquantel through preferential crystallization of a conglomerate cocrystal

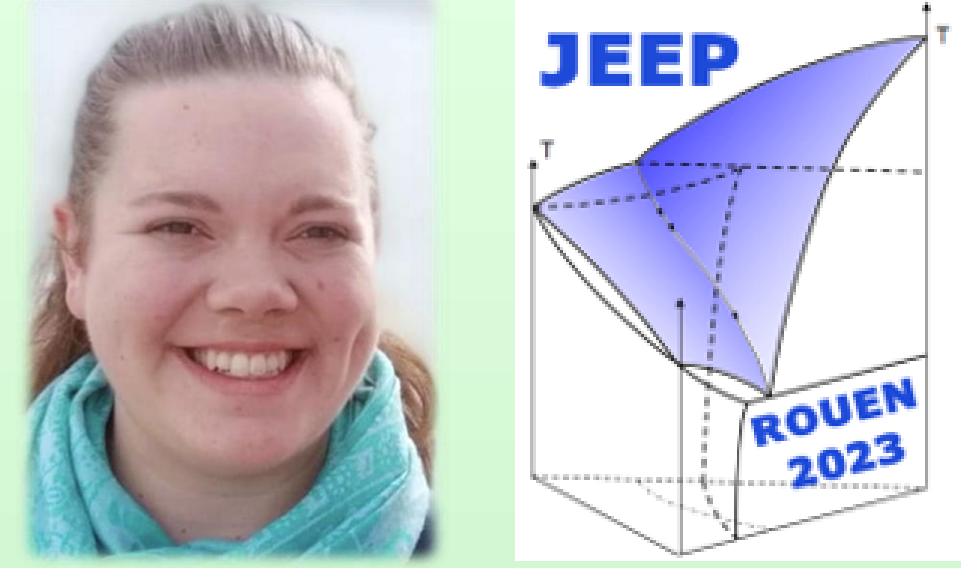
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INTRODUCTION

Praziquantel (PZQ)

Racemic compound

Coformer [1]: Vanillic acid (VA)

Racemic compound

Equimolar

Non equimolar

Intensity (A.U.)

2θ (°)

SHG-Microscopy

PZQ:VA

PZQ:2VA

Temperature [°C]

x_{VA}

Isoplethal binary section [2]: [R-PZQ] = [S-PZQ]

Temperature [°C]

x_{VA}

Temperature [°C]

x_{VA}

Temperature [°C]

x_{VA}

Temperature [°C]

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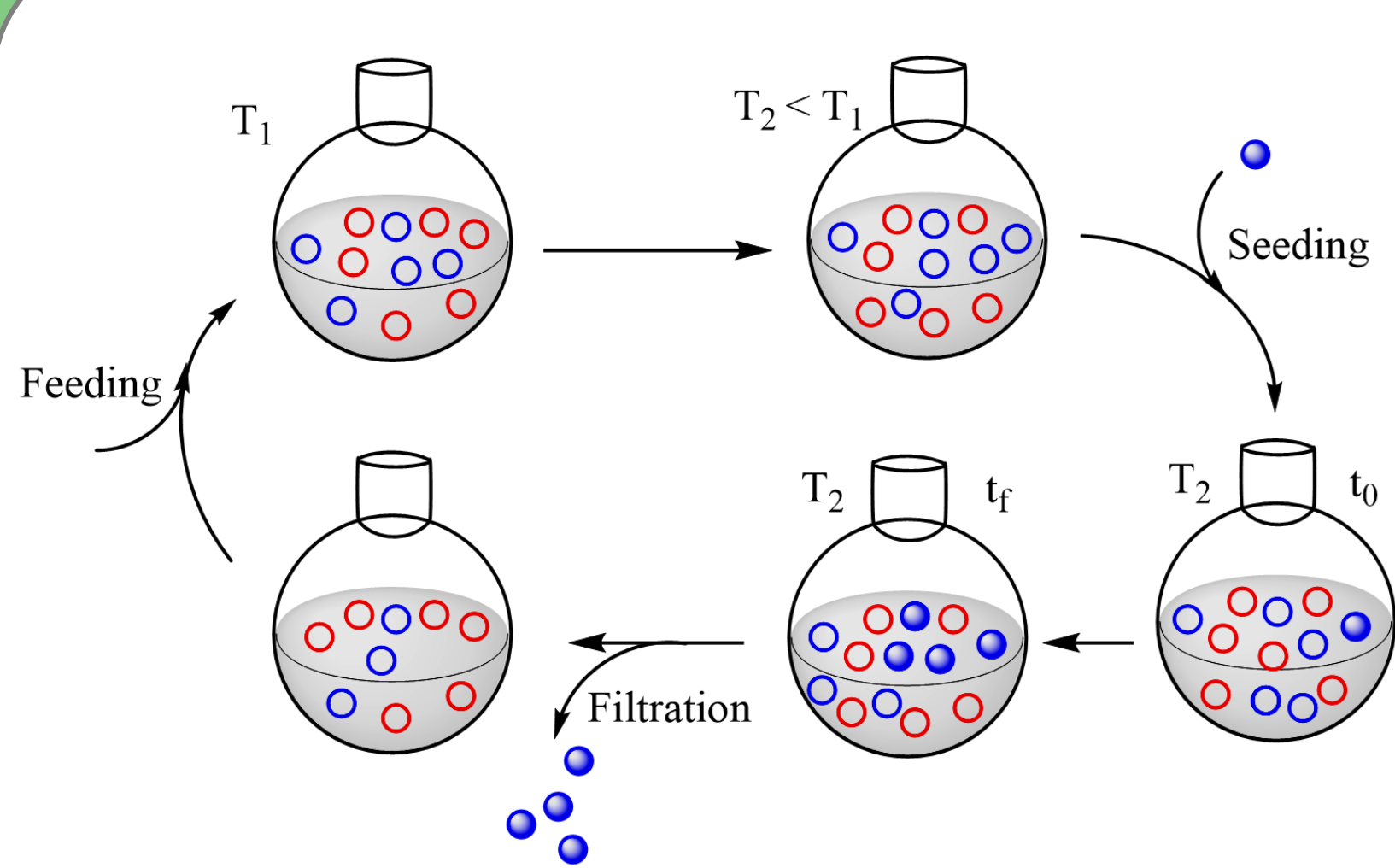
Temperature [°C]

x_{VA}

OBJECTIVES

Perform the preferential crystallization of the conglomerate cocrystal PZQ:2VA to obtain enantiopure PZQ

PREFERENTIAL CRYSTALLIZATION

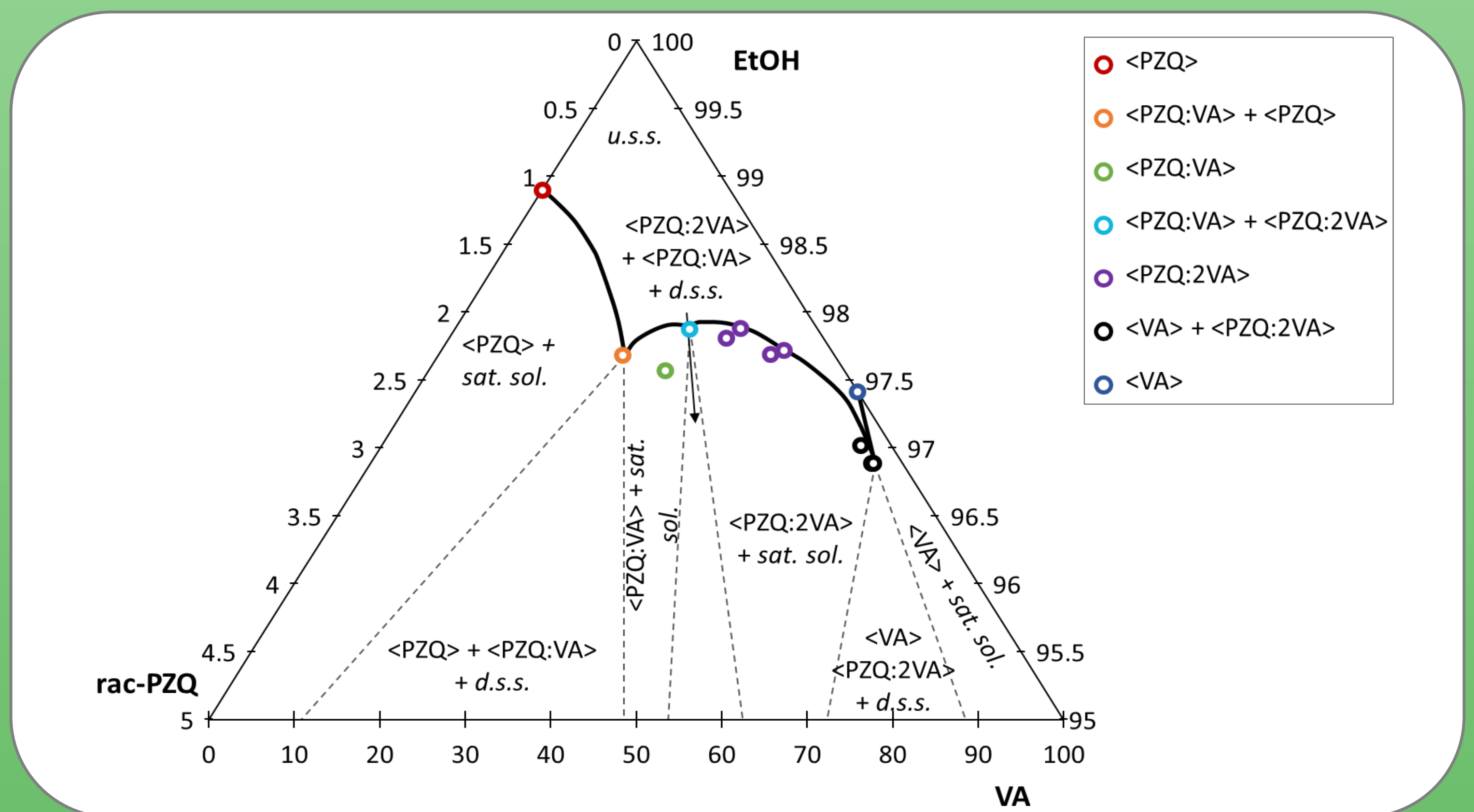


From a metastable supersaturated racemic solution, nucleation of the eutomer is stereo-selectively triggered through secondary nucleation, by seeding the solution with crystals of the eutomer.

The solution remains metastable regarding primary nucleation, therefore only crystals of the eutomer nucleate and grow in the solution.

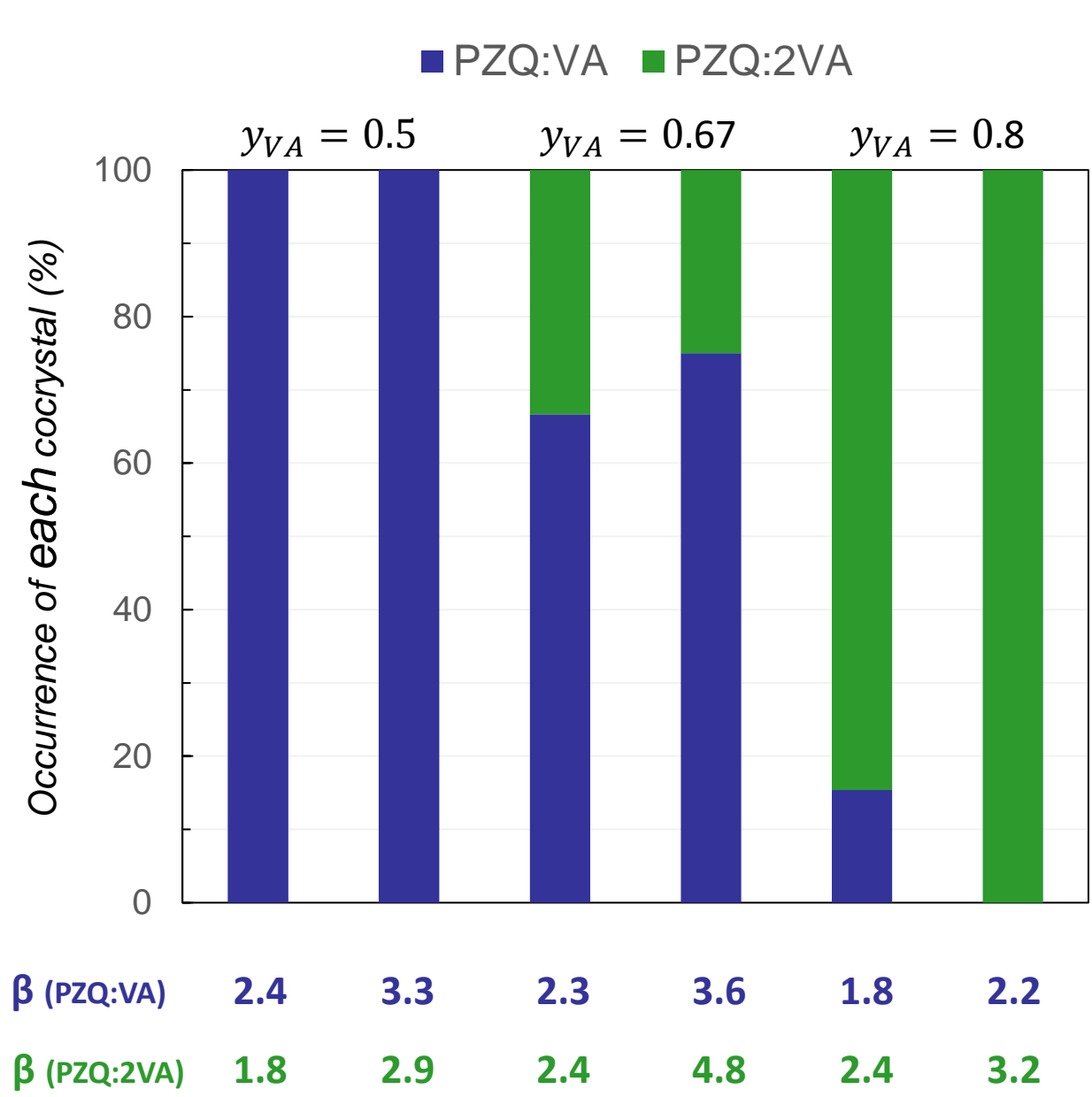
After filtration, the eutomer is recovered. The process can then be cycled.

SOLUBILITY AT 20°C



CRYSTALLIZATION BEHAVIOR

Probability of nucleation of each cocrystal regarding the solvent-free molar ratio of VA



Kinetics favors PZQ:VA (racemic compound) at the expense of PZQ:2VA (conglomerate), even if PZQ:2VA is the most stable

Need VA enrichment to promote PZQ:2VA nucleation [3]

SCREENING OF PC CONDITIONS

Mass of seed

Volume (mL)	β	Mass of seed (mg)	Solid enrichment
20	2.2	2	No
20	2.2	50	Yes
20	2.2	100	Yes

➔ m_{seed} ≥ 50mg

Supersaturation

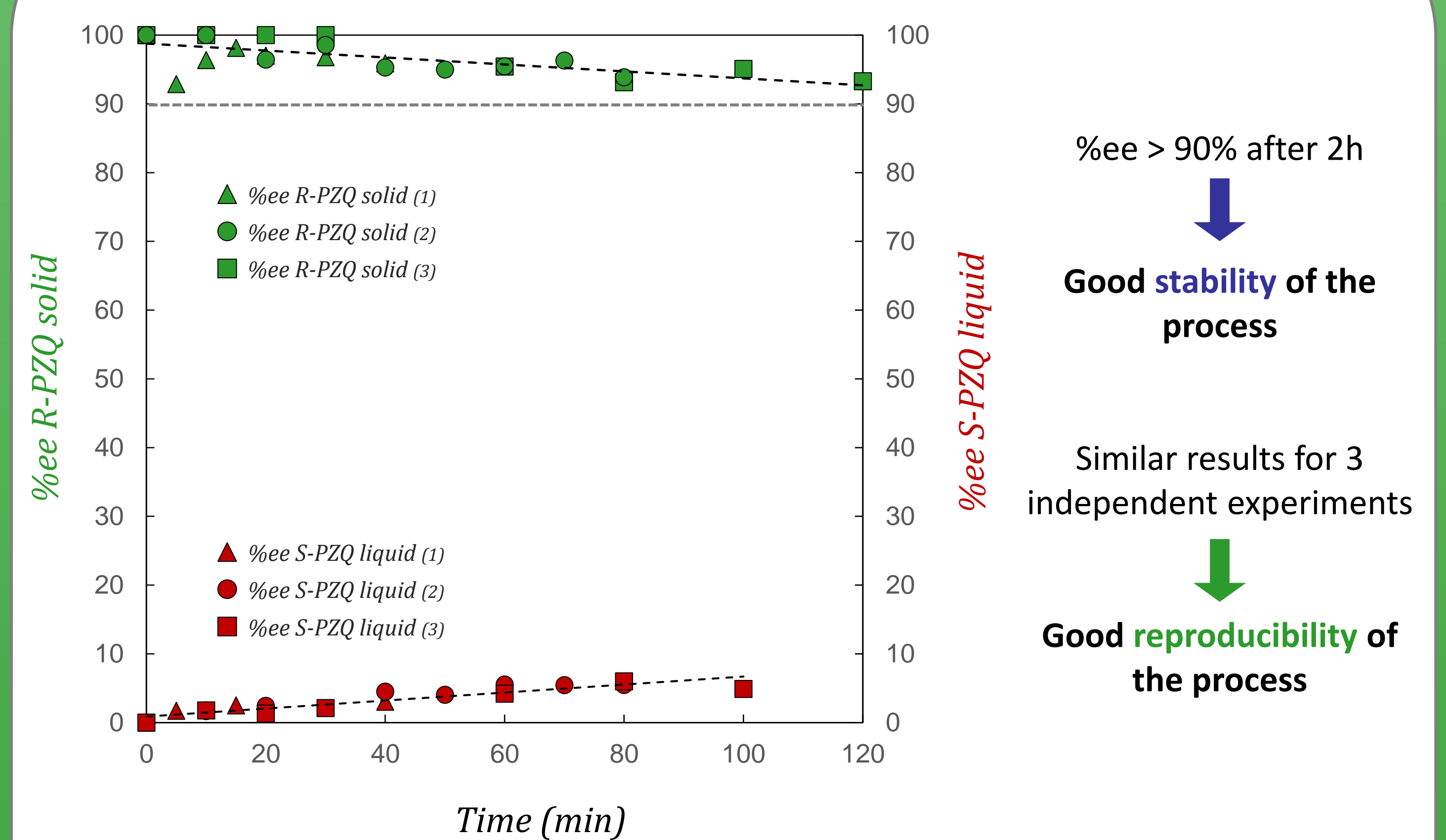
Volume (mL)	β	Mass of seed (mg)	Solid enrichment
20	2.2	50	No
20	1.5	50	Yes
20	1.25	50	Yes

➔ β ≤ 1.5

Conditions: V = 20mL
β = 1.25
m_{seed} = 50mg

RESULTS

Seeding with enantiopure R-PZQ:2VA



Washing in acidic media (pH<3) and extraction with dichloromethane

%ee > 90% after 2h

Good stability of the process

Similar results for 3 independent experiments

Good reproducibility of the process

CONCLUSION

Identification and crystallization of a conglomerate cocrystal of PZQ

The preferential crystallization of the conglomerate cocrystal PZQ:2VA has been achieved

The final enantiomeric excess of R-PZQ obtained is > 90%ee

The process is reproducible and stable over at least 2h

PERSPECTIVES

Cycle the process (successive crystallization of R-PZQ and S-PZQ)

Scale-up

[1] Devogelaer, J. J. et al. (2021). Cocrystals of Praziquantel: Discovery by Network-Based Link Prediction. *Crystal Growth & Design*, 21(6), 3428-3437

[2] Gerard, C. J. J. et al. (to be published). Phase diagrams of Praziquantel and Vanillic acid cocrystals: racemic compound and conglomerate system

[3] Gerard, C. J. J. et al. (to be published). Direct chiral resolution of praziquantel via preferential crystallization of a conglomerate cocrystal