





## PhD position at the University of Rouen-Normandie

# Laboratory "Sciences et Méthodes Séparatives" : http://labsms.univ-rouen.fr

## **Project : IPOCRAC**

### (ImPrOving preferential Crystallization by RAcemisation and Co-crystallization)

In the pharmaceutical industry, **50% of the marketed drug compounds contain a chiral center**<sup>1</sup>. Most often, one enantiomer has the desired pharmacological effect, the other might be inactive or have adverse effects. It is therefore necessary to **access the desired enantiomer**. Resolution by crystallization is often preferred over other methods (such as asymmetric synthesis or chromatographic techniques) due to low cost and carbon footprint. Among them, Preferential Crystallization (**PC**) is the process by which the out-of-equilibrium crystallization of a single enantiomer from a racemic mixture is triggered by seeding. PC is an efficient process that can be cyclized but which treat the unwanted enantiomer as an impurity so that the yield cannot exceed 50%<sup>2</sup>. Yet, if the compound of interest (or an intermediate) is **racemizable**, the unwanted enantiomer can be reconverted into a racemic mixture (Figure 1), allowing a theoretical improved **100% yield** and a better productivity compared to PC.<sup>3</sup>



Figure 1 : Schematic view of a deracemization process

"Deracemization processes" rely on racemization and involve the creation of an imbalance between the two enantiomers in the solid phase, giving rise to enantiopure crystals. The enantiomer imbalance can have a kinetic nature<sup>4-6</sup>, or a thermodynamic nature <sup>7, 8</sup>).

Nevertheless, all these crystallization processes, <u>suffer from a major limitation</u>: the pair of enantiomers should naturally crystallize into separate crystals; such situation is termed as "**conglomerate**" and is only rarely encountered (5% occurrence) (Figure 2). In order to circumvent this issue, a screening procedure of new solid phases is commonly performed, most often involving the formation of salts, up to the identification of a suitable conglomerate.





*Figure 2: Schematic representation of the crystallization behavior of a racemic mixture.* 

**Co-crystals** are new solid phases resulting from the association of two (or more) crystallization partners (e.g. *S* or *R* enantiomers with an achiral co-former). If the new obtained solid phase is conglomerate, the cocrystallization can therefore be seen as a strategy to force two enantiomers to crystallize separately. Co-crystal phase screening is most often performed by high energy milling applied to the racemic mixture of target enantiomers with various achiral coformers (Figure 3). Yet, the SMS team and the team of Prof. Leyssens (UCLouvain) published recently (almost concomitantly) the first two examples of **PC** using conglomerate co-crystals.<sup>9,10</sup>



# The objective of the IPOCRAC project is to propose an original way to resolve chiral co-crystals by performing deracemization under high energy milling conditions.

This project gather two innovative approaches (Figure 4) : i) the **PC** of chiral co-crystals that we recently developed in the SMS lab as described above and ii) a mechanochemical approach consisting in grinding the target enantiomeric mixtures using high energy milling in the presence of a small amount of solvent (liquid assisted grinding, LAG) in order to overcome the high energy barrier required for enantiomer interconversion (racemization).









Figure 4 : Schematic representation of the process that would be developed in the IPOCRAC project



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### Candidate profile :

Master 2 or engineer with a speciality focuses on solid chemistry, materials chemistry, Crystallisation, Pharmaceutical/organic solids.

Mandatory skills (to be mentioned in the cover letter):

- Ease with experimental work
- English spoken, read and written
- Good oral and written communication
- Experience in a laboratory research (at least 6 months cumulated during education)

### Other skills (at least two):

- Management of Solid-state Characterization
- Knowledge on Organic Solid State
- Phase Diagram Determination









- Working Knowledge in Organic Chemistry
- Experience in a lab (at least 6 months cumulated)

Document to transmit to the supervising team

- Detailed CV
- Cover letter highlighting your adequation with the subject
- Transcript of master's grades (M1 and M2)
- One or two referent people to contact

During the PhD, travels and stays with our partner in UCLouvain-Belgium will be organized.

After the selection of candidates, an oral interview will be organized.

Type of funding : Région NORMANDIE

**Supervising team** (please send your application to all members) : <u>valerie.dupray@univ-rouen.fr</u>, <u>yohann.cartigny@univ-rouen.fr</u>, clement.brandel@univ-rouen.fr

