Secteur des Sciences et Technologies

Invitation à la soutenance publique de thèse de

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Master 120 en Sciences chimiques à finalité spécialisée

Pour l'obtention du grade de Docteur en sciences

« Nefiracetam Solid Forms : from Physicochemical Properties Enhancement by Cocrystallization to Chiral Resolution through Preferential Crystallization »

qui se déroulera
le lundi 16 novembre 2020 à 10h
En visioconférence
1348 Louvain-la-Neuve

Jury members :

Prof. Tom Leyssens (UCLouvain), supervisor
Prof. Yann Garcia (UCLouvain), chairperson
Dr. Koen Robeyns (UCLouvain), secretary
Prof. Sophie Hermans (UCLouvain)
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Dr. Luc Aerts (UCB Pharma)
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The pharmaceutical industry has always faced challenges. Some of these challenges relate directly to the physicochemical properties of the drug compounds. Poor water-solubility, dissolution rate, and permeability are among the main issues encountered during drug development. Issues related to these may ultimately result in failure during drug development. A second well-known issue relates to the chirality of the drug compound, with both enantiomers often presenting different biological effects. It is therefore recommended to aim for single enantiomer formulations of drug forms to avoid a crisis such as encountered for thalidomide. Classical approaches to produce single enantiomers involve asymmetric synthesis or chiral resolution of a racemate. In this work, we aim at resolving both issues through a crystal engineering approach, more precisely focusing on cocrystallization. On one hand, we use cocrystals to improve the physicochemical properties of nefiracetam, a target drug compound, and on the other, we use cocrystals of nefiracetam to develop a resolution process of mandelic acid through preferential cocrystallization. Nefiracetam is a lipophilic, nootropic drug of the racetam family. We attempted to tune the solubility of this compound using a cocrystal approach. Prior to doing so, a preliminary polymorph screening was performed as this was absent in the literature. To our surprise, we were able to identify polymorph FII, stable at higher temperatures, and thus enantiotropically related to form FI, stable at low temperatures. A third metastable form was also discovered recrystallizing nefiracetam from the melt. Finally, a monohydrate form was identified working in water saturated conditions. These novel solid forms of nefiracetam were structurally and thermodynamically analyzed, with the solubility of the monohydrate evaluated as reference, since we showed a rapid solvent-mediated conversion to this form in solution. We then set out, to explore the potential of nefiracetam cocrystals screening 133 coformers among which carboxylic acids, amino acids, profens, racetams and sugars. Seventeen of these led to successful cocrystal formation, with a high success rate for carboxylic acid containing coformers. Among the cocrystals, three are biocompatible (citric acid, oxalic acid and zinc chloride) and more deeply studied. To be based on dissolution experiments, the nefiracetam-citric acid cocrystal appeared a potential candidate for formulation of nefiracetam. During cocrystal screening, we stumbled upon a remarkable result. Indeed, a cocrystal between nefiracetam and mandelic acid was identified. Not only pharmaceutically interesting, as mandelic acid shows analgesic, antirheumatic and spasmolytic effects, cocrystallization seemingly led to formation of a stable conglomerate, whereas mandelic acid forms itself a racemic compound. We fully characterized this system, to then develop a chiral resolution of mandelic acid by entrainment. Different modes of this process were developed such as the Seeded Isothermal Preferential Crystallization (SIPC) and the Seeded Polythermal Preferential Crystallization (S3PC) modes all leading to excellent entrainment results showing relatively good yields per cycle, and more importantly enantiopure outcome.