POLITECNICO DI MILANO

PhD in CHIMICA INDUSTRIALE E INGEGNERIA CHIMICA / INDUSTRIAL CHEMISTRY AND CHEMICAL ENGINEERING - 38th cycle

PNRR_352 Research Field: CO-CRYSTALLIZATION APPROACHES FOR IMPROVING PHYSICOCHEMICAL PROPERTIES OF ACTIVE PHARMACEUTICAL INGREDIENTS

Monthly net income of PhDscholarship (max 36 months)
€ 1325.0 In case of a change of the welfare rates during the three-year period, the amount could be modified.

Context of the research activity	
Motivation and objectives of the research in this field	Co-crystals are at the forefront of the quest for novel solid forms of active pharmaceutical ingredients (APIs). The great potential of co-crystals resides in their usually different physicochemical properties (such as solubility, dissolution rate, melting point, color, etc.) compared to those of the single components. In addition, and more relevant to pharma industries, the process of co-crystal formation involving an API does not compromise the chemical integrity of the API itself, and, furthermore, a new co-crystal may be patented as an entirely new crystalline species, whose physicochemical properties may be completely different from the ones of the pure API.At the SBNLab, we have unique and world-class expertise in crystal engineering, molecular recognition, and supramolecular chemistry. The project will involve also the collaboration of the Crystal Engineering Laboratory of the University of Limerick. In the context of the present project, we have patented and published a new co-crystal of 3-iodo-2-propynyl-N-butylcarbamate (IPBC), a wide-spread biocide, with CaCl2. Indeed, we demonstrated that CaCl2 rapidly forms a 1:4 co-crystal with IPBC (10% w/w), yielding improved physicochemical properties, such as higher melting point and thermal stability, and better powder free-flowing properties. Furthermore, the co-crystal synthesis was obtained fully in the solid state by ball milling and the process was scaled-

	up in an attrition mill yielding on the order of kilogram.In this proposal, we suggest an approach based on using FDA approved co-crystal formers (CCFs), mainly salts, yielding new ionic co-crystals of selected APIs to improve their physicochemical properties, such as thermal stability, water solubility, and powder free-flowing properties, thus overcoming the challenges that limit the use of several APIs. This would contribute to enrich the library of APIs actually employable for the development of new drugs and therapeutic strategies, in line with the PNRR mission for Human Health. Moreover, such an approach may easily be scaled-up by using mechanochemistry, *i.e.*, milling or grinding, without the need for bulk dissolution of reactants. Mechanochemistry is ¿green¿ and sustainable and it is suitable for industrial purposes where large-scale clean, safe, and efficient transformations are needed.
Methods and techniques that will be developed and used to carry out the research	The project is organized in four tasks, as detailed in the following sections:*Task 1: Supramolecular synthon identification.*Task 1 aims at designing and identifying the key supramolecular synthons occurring between the selected APIs and the FDA approved CCFs. At this aim, careful data mining in the Cambridge Structural Database CSD will allow us to evaluate and identify the most likely interaction patterns between the CCFs and the APIs. *Task 2: Ionic co-crystal formation and screening on laboratory scale.* The Task 2 will be dedicated to the co-crystal formation and the screening of the experimental conditions aiming at selecting the proper ratio between the API and the CCF. In addition, in this Task the possible formation of new drug polymorphs will also be investigated. Co-crystal synthesis will first be carried out using different conditions such as dry milling, liquid-assisted grinding, *i.e.*, adding a few drops of different solvents, as well as different milling speed and time conditions.*Task 3: Physicochemical properties evaluation.*This task will be focused on the evaluation of the physicochemical properties of the new ICCs obtained in the Task 2. Specifically, we will evaluate the thermal stability of the developed ICCs by DSC and TGA analyses. The powder free-flowing behavior will be assessed by measuring the angles of repose. Chemical

	and physical stabilities will be determined by using accelerated tests in specific environmental chambers. Crystallinity, particle size, morphology, identification of amorphous fraction, and surface area will be determined by X-ray diffraction and microscopy methods (such as POM, TEM, SEM, and AFM). Hygroscopicity, solubility in water, and dissolution properties will be determined according to Olon formulation needs.*Task 4: Scale-up of ICCs via mechanochemical synthesis.* This task will be dedicated to the scale-up of the mechanochemical synthesis of the most promising new ionic co-crystals developed and characterized in the former Tasks. The selection of the selected new solid forms to be up-scaled and it will be done in close cooperation with Olon researchers. All of the produced co-crystals will be characterized by DSC, IR, TGA, NMR or SSNMR, and Single Crystal and Powder X-Ray diffraction analysis to demonstrate the identity and the purity of the obtained phases optimized.
Educational objectives	The proposed PhD program will provide an excellent training program to the PhD candidate, who will acquire advanced skills in crystal engineering and pharmaceutics fields. Moreover, the PhD candidate will be trained to become and independent scientist, able to conduct original research, through the acquisition of multidisciplinary competencies and methodological expertise. Through the stay at the University of Limerick, the candidate will develop as the ability to work in an international team and to effectively communicate research achievements in different environments.
Job opportunities	Through the creation of a network between the academic community and industrial companies operating in the field, the proposed PhD project will set the bases for future research-oriented careers at either university or industry in the field of multi-components pharmaceutical materials.
Composition of the research group	2 Full Professors 3 Associated Professors 5 Assistant Professors 4 PhD Students
Name of the research directors	Prof. P. Metrangolo, Prof. G.Terraneo

Contacts
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Additional support - Financial aid per PhD student per year (gross amount)	
Housing - Foreign Students	--
Housing - Out-of-town residents (more than 80Km out of Milano)	--

Scholarship Increase for a period abroad	
Amount monthly	662.5 €
By number of months	6

National Operational Program for Research and Innovation	
Company where the candidate will attend the stage (name and brief description)	Olon (https://olonspa.com/)
By number of months at the company	6
Institution or company where the candidate will spend the period abroad (name and brief description)	University of Limerick, Ireland
By number of months abroad	6

Additional information: educational activity, teaching assistantship, computer availability, desk availability, any other information

Confidentiality: since this is a thematic scholarship, the management of Confidential Information, Results and their publication is subordinate to the restrictions agreed upon with the funding company. Upon acceptance of the scholarship, the beneficiary must sign a specific commitment.

Individual budget for research (during the 3 years): about 5.400 euro

Teaching assistantship: availability of funding in recognition of supporting teaching activities by the PhD student. There are various forms of financial of for activities of support to the teaching practice. The PhD student is encouraged to take part in these activities within the limits allowed by the regulation.