FINAL SCIENTIFIC REPORT

PD 45/2020

From amorphous to crystalline: in the quest for new pharmaceutical formulation, with improved stability of representative statin drugs (CryStatin)

Improving the bioavailability of poorly soluble drugs for oral administration remains one of the most challenging aspects of the drug development process. Amorphous forms create problems at the formulation stage, they have inferior rheological properties than crystalline systems. In this context, the aim of the project is to explore the possibility of obtaining new crystalline solid forms for representative active substances of the statin class with better solubility. Coformers (pharmaceutically approved compounds) and a set of high-throughput parallel crystallisation experiments were used to achieve this objective. Specific project objectives:

O1. Establish the co-crystallization behaviour and complete structural characterization of Pitavastatin

O2. Establish the co-crystallization behaviour and complete structural characterization of Pravastatin

To achieve the two objectives the following Specific Activities were carried out:

O1.: 1.1. Determination of the solubility profile for Pitavastatin; 2.1 Determination of the solubility profile for Pravastatin; 2.2 Rational design for co-crystal pharmaceutical formation of Pitavastatin; 2.3 Co-crystallization experiments for Pitavastatin; 2.4 New solid forms identification through XRD or SC for samples resulting from the co-crystallization experiments of Pitavastatin; 2.5 Scale-up of the new solid forms of Pitavastatin; 2.6 Crystal structure determination for the new solid forms of Pitavastatin; 2.7 Dissolution and stability experiments for the new solid forms of Pitavastatin; 2.8 - Dissemination of results; 2.9 Project Management;

O2.: 3.1 Rational design for co-crystal pharmaceutical formation of Pravastatin; 3.2 Co-crystallization experiments for Pravastatin; 3.3 New solid forms identification through XRD or SC for samples resulting from the co-crystallization experiments of Pravastatin; 3.4 Scale-up of the new solid forms of Pravastatin; 3.5 Crystal structure determination for the new solid forms of Pravastatin; 3.6 Dissolution and stability experiments for the new solid forms of Pitavastatin and Pravastatin; 3.7 Dissemination of results; 3.8 Project Management;

For each activity, Experiment reports have been prepared in which all experimental details and results are fully presented.

The most relevant result is the obtaining of Pitavastatin tert-Butylamine salt. This new solid form was obtained from the *Vapor diffusion on liquids crystallization experiment*. An experimental protocol was defined for this sample and it was obtained at large scale (Figure 1). The solubility of Pitavastatin and Pitavastatin tert-Butylamine salt was evaluated by a non-phelometric optical method (Figure 2).

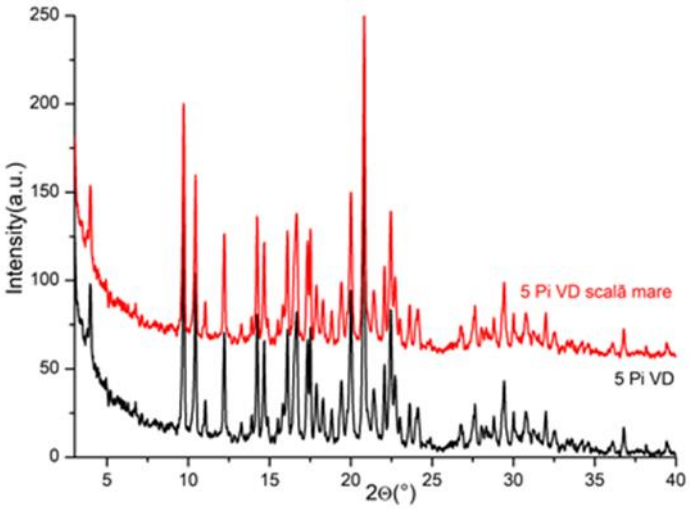

Figure 1. X ray diffraction patterns of Pitavastatin tert-Butylamine salt (5 Pi VD) and Pitavastatin tert-Butylamine salt scale-up (5 Pi VD scală mare)

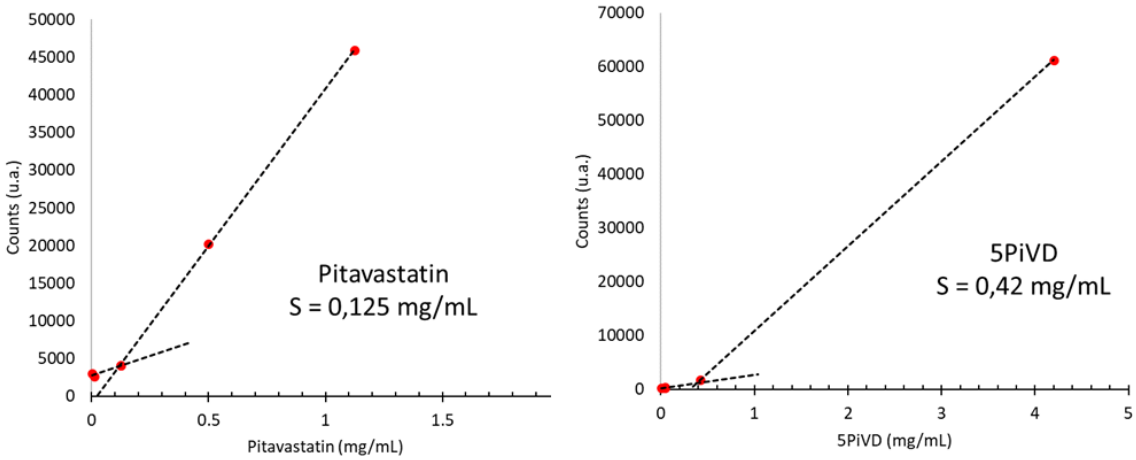

Figure 2. Results obtained for solubility of Pitavastatin and Pitavastatin tert-Butylamine salt (5 Pi VD)

The aim of the project was to obtain new crystalline solid forms for representative active pharmaceutic substances from the statin class with better solubility than commercially available amorphous forms. Obtaining the crystalline solid form - Pitavastatin tert-Butylamine salt - with a solubility 4 times higher than that of Pitavastatin demonstrates that this project was successfully implemented.

Indicators fulfilled:

- *Experimental reports*: for each activity an Experiment Report was accomplished
- *Structures reported in databases*: The Cambridge Structural Database 2178475, 2178476, 2303824, 2303825.
- *Activity reports*: 3 reports reported
- *Website*: Design, populating and updating the project website https://www.itim-cj.ro/PNCDI/crystatin
- *International conferences*: - Participation at international conference ISI indexed: Miclaus M, Grosu I, New crystalline forms with improved stability of representative statin drugs, 12th

International Advances in Applied Physics & Material Science Congress & Exhibition, Oludeniz, Turkey, 2022

- - Participation at international conference ISI indexed: Miclaus M, Grosu I, Filip X, Crystalline salt of amourphous drug, 13th International Advances in Applied Physics & Material Science Congress & Exhibition, Oludeniz, Turkey, 2023

Scientific ISI papers: - *Scientific* paper with title Exploring the polymorphism of selective androgen receptor modulator YK11, Journal of Molecular Structure, Alexandru Turza, Gheorghe Borodi, Maria Miclaus, Marieta Muresan-Pop, Volum 1273, ID 134281, doi: 10.1016/j.molstruc.2022.134281. (impact factor year 2021 - 3,841)

- - *Scientific* paper sent (under revision) with title Exploring the crystal and molecular structure of methenolone and drostanolone enanthate, Zeitschrift fur Kristallographie-Crystalline Materials, Alexandru Turza, Maria Miclaus, Gheorghe Borodi

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