Activity report 2021

Project PD 45/2020

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

Stage summary

In this stage of the project, the following activities have been performed: 2.1 Determination of the solubility profile for Pravastatin; 2.2 Rational design for the formation of pharmaceutical co-crystals of Pitavastatin; 2.3 Experimental reports (Co-crystallization experiments for Pitavastatin); 2.4 Identification of new solid forms through XRD and SC for the samples obtained from the co-crystallization experiments for Pitavastatin; 2.5 Scale-up preparation of new solid forms of Pitavastatin; 2.6 Determination of the crystalline structure for the new solid forms of Pitavastatin; 2.7 Stability experiments and determination of the dissolution rate for the new solid forms of Pitavastatin; 2.8 - Dissemination of results.

Here are the results obtained for each activity:

2.1 Determination of the solubility profile for Pravastatin

Following the solubility experiments, it was observed that Pitavastatin is soluble in most of the solvents used, but it tends to form an oily solution, and after the evaporation of the solvents/mixtures, only two samples were obtained in powdered form. Analyzing the X-ray diffractograms, it was observed that the two analyzed samples have significantly higher crystallinity compared to the starting compound.

2.2 Rational design for the preparation of pharmaceutical co-crystals of Pitavastatin

Based on the solubility profile of the active pharmaceutical compound, Pitavastatin, various crystallization and co-crystallization methods were selected. The number of experiments corresponding to each crystallization and co-crystallization method was correlated with the number of solvents within the relevant solubility domains. The following crystallization and co-crystallization methods were chosen: *Cooling crystallization*, *Anti-solvent vapor diffusion crystallization in liquids*, *Vapor diffusion crystallization in liquids*, *Mechanical mixing with solvent - ball milling*, *Solvent-assisted grinding*.

2.3 Experimental reports (Co-crystallization experiments for Pitavastatin)

After defining the experimental design, the crystallization and co-crystallization experiments described above for Pitavastatin were carried out, and experimental reports were written.

2.4 Identification of new solid forms through XRD and SC for the samples obtained from the co-crystallization experiments for Pitavastatin

The solids obtained in powdered form from the crystallization and co-crystallization experiments described in activity 2.3 were analyzed using X-ray powder diffraction (XRD) to identify any new solid forms or the starting compound with improved crystallinity. The most significant results were obtained from the following experiments:

- Cooling *crystallization* - improved crystallinity in solvents: acetone H2O (8:2), methanol: H2O (8:2) and 2-Methylpentane;
- *Vapor diffusion crystallization in liquids* - two salts with tert-Butylamine and Diethylamine were formed.
- *Solvent-assisted grinding* - a salt of Pitavastatin with Sodium acetate.

2.5 Scale-up preparation of new solid forms of Pitavastatin

From the crystallization and co-crystallization experiments, three salts with tert-Butylamine, Diethylamine, and Sodium acetate were obtained. A protocol was defined for each type of experiment to produce them on a larger scale. XRD analysis confirmed that these new solid forms are reproducible at a larger scale.

2.6 Determination of the crystalline structure for the new solid forms of Pitavastatin

To determine the crystalline structure models by analyzing the X-ray powder diffraction data, a specific methodology was followed for two of the new solid forms obtained. After introducing the experimental parameters and primary processing of the experimental diffraction pattern, representative diffraction intensities were selected for indexing the experimental diffraction patterns. For the two samples analyzed, the Rwp figure of merit factor was obtained, with a high value. Therefore, it was concluded that the investigated samples are not sufficiently crystalline to determine the crystal structure from powders.

2.7 Stability experiments and determination of the dissolution rate for the new solid forms of Pitavastatin

In the development of pharmaceutical compounds, tests of physicochemical stability are of major importance. Particularly, the stability of the new solid forms has significant implications

in the production and storage process of orally administered medications. In this activity, an accelerated stability testing procedure was used by subjecting the samples to high temperature and humidity (in accordance with International ICH Guidelines). The sample of interest was kept in a climatic chamber of type Memmert HCP 108 at a temperature of 40°C and relative humidity RH=75%, and it was analyzed by X-ray diffraction at specific time intervals to observe any structural changes. By comparing the diffractograms, it was concluded that the sample (Pitavastatin salt with Sodium acetate) remained stable over time after exposure to high temperature and humidity.

2.8 - Dissemination of results

In the current stage, in addition to the experimental work, the design and preparation of the experimental reports have been completed, and all the specified indicators have been achieved:

- Design, content and update of the project website https://www.itim-cj.ro/PNCDI/crystatin

- Scientific article, 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)

- 1 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.

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