Activity report 2023

Proiect 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: 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.

Here are the results obtained for each activity:

Activity 3.1 - Rational design for co-crystal pharmaceutical formation of Pravastatin

The following crystallization and co-crystallization methods were chosen for the compound Pravastatin: Cooling Crystallization, Crystallization by co-dissolution and slow evaporation, Vapor diffusion crystallization in liquids, Crystallization by mechanical mixing with solvent - ball mill.

Activity 3.2 - Co-crystallization experiments for Pravastatin

Four types of experiments were carried out using a variety of solvents/solvent mixtures, co-formers and different experimental conditions.

Activity 3.3 - New solid forms identification through XRD or SC for samples resulting from the co-crystallization experiments of Pravastatin

After analysis of the XRD data, for Cooling crystallization experiments, where obtained samples with improved crystallinity 1, 2, 3, 5, 8 and 9 Pra Na. These samples were prepared in the solvents Tetrahydrofuran, Ethanol, 2,2,2-Trifluoroethanol, Acetone:H2O (8:2), Acetone and Methanol. The highest crystallinity was obtained for sample 1 Pra Na cryst.

Four new solid forms were obtained from the co-dissolution and slow evaporation crystallization experiments for the compound Pravastatin: 3 Pra A (co-crystallization with Diethylamine), 8 Pra A (co-crystallization with Oxalic acid), 9 Pra A (co-crystallization with Fumaric acid) and 10 Pra A (co-crystallization with Adipic acid).

Following the Vapor diffusion crystallization in liquids experiments for the compound Pravastatin sodium samples 3 Pra Na VD, 5 Pra Na VD, 6 Pra Na VD and 9 Pra Na VD have been analyzed by XRD, the

other samples were in the form of glue and could not be analysed. No new solid forms were obtained from this experiment.

Eight experiments of Crystallization by mechanical mixing with solvent - ball mill were performed and analyzed by XRD. The experiments resulted in a new solid form with Sodium carbonate anhydrous - samples 3 Pi G1 and 4 Pi G1.

Activity 3.4 - Scale-up of the new solid forms of Pravastatin

Two new solid forms 9 Pra A and 5 Pra Na G1 were selected for this work to be reproduced at large scale. For each sample a protocol was defined. After analysis of the X-ray diffraction data it results that the two new solid forms were obtained at large scale.

Activity 3.5 - Crystal structure determination for the new solid forms of Pravastatin

For crystal structure determination from X-ray diffraction patterns we have gone through the following steps: proper sample preparation, adjustment of experimental parameters and recording of a high resolution diffraction pattern, introduction of experimental parameters, indexing of the diffraction pattern, determination of the space group, Pawley refinement [6], search for preliminary structural models using computational algorithms, refinement using the Rietveld method.

For two of the obtained new solid forms (9 Pra A and 5 Pra Na G1) we applied crystal structure determination.

Crystal structure determination by X-ray diffraction on powder for 9 Pra A:

To obtain the best results from the indexing process the following programs were applied: DICVOL91, TREOR90 and X-Cell. The best results were obtained after indexing with DICVOL91. The chosen structural solution was a= 14.1099, b= 12.836, c= 7.638, α= 8.338, λ= 38.527, β= 144.925, γ= 136.357, triclinic crystallographic system. The search for a structural model was carried out using the computational algorithm, Simulated Annealing. Following Rietveld refinement, a crystallographically acceptable figure of merit was not obtained

Crystal structure determination by X-ray diffraction on powder for 5 Pra Na G1:

To obtain the best results from the indexing process the following programs were applied: DICVOL91, TREOR90 and X-Cell. Following the indexing process, no realistic cell parameters were obtained with any of the programs listed above. From this it was concluded that the investigated sample is not crystalline enough to be able to determine the crystal structure from powder.

Activity 3.6 - Dissolution and stability experiments for the new solid forms of Pitavastatin and Pravastatin

In the development process of pharmaceutical compounds, physicochemical stability tests are of major importance. In particular, the solid-state stability of new solid forms has important implications for

the production and storage of orally administered medicinal products. In this work an accelerated stability testing procedure was used, by exposure to elevated temperature and humidity (in accordance with the International ICH Guidelines). The two samples were subjected to experimental conditions and tested at certain time intervals to see if structural changes occur. By comparing the diffraction patterns we concluded that the two samples are stable after three months of exposure to high temperature and humidity.

Solubility assessment

The solubility of 10 Pi G1, 5 Pi VD and 7 Pi VD preparations was evaluated by a non-phelometric optical method. An optical system equipped with a Silver Nova CCD simultaneous detector (Ocean Optics, USA) was used and experiments were performed at a wavelength of λ=660 nm with integration time 500 ms. Solubility testing was performed in distilled water.

While the solubility of the 7 Pi VD and 10 Pi G1 preparations was weaker than the Pitavastatin standard, the 5 Pi VD compound showed a nearly 4-fold increase in solubility.

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