Results of stage 1 (2017)

Mycotic infections represent a serious medical issue due to the: (1) increasing frequency, (2) development of multi-drug resistance of different pathogenic strains, (3) the need for long-term treatment of deep infections or hair and nails infestations, which causes (4) accumulation and toxicity at hepatic level. Ketoconazole (KET) was the first wide-spectrum oral antifungal, but with low solubility in water. Previously to this project we have obtained two co-crystals of KET, ketoconazole-fumaric acid (KET-FUM) and ketoconazole-*p*-aminobenzoic acid (KET-PABA), with improved solubility compared to ketoconazole (KET-FUM 100 times greater than KET and KET-PABA 10 times greater). In this project we aimed to evaluate their pharmacological potential by completing the preliminary data with common or specific studies for each solid form. Thus, during the 6 activities carried out, the following results were aquired:

1. ***Structural characterization of KET-PABA***. Within *A.1.1* activity this compound was obtained as single-crystal, and within *A.1.3* activity, by combining single-crystal X-ray diffraction techniques and solid state NMR spectroscopy with molecular calculations, its structural characterization was performed. KET-PABA crystallised in the triclinic space group P-1/c. The crystalline structure contains ketoconazole and *p*-aminobenzoic acid in a 1:1 ratio, an important feature of this structure being the delocalization, even at low temperature, of three carbon atoms and the presence of a strong hydrogen bond.

2. ***For KET-FUM co-crystal***, which has pharmacological potential for oral therapy, within *A.1.4* activity ***compatibility studies with the most frequently pharmaceutical excipients, used in the preformulation of commercial Ketoconazole,*** were performed. The employed excipients were: hydroxypropyl methylcellulose (Hypromellose K4M), corn starch (CSt), magnesium stearate (MgSt), lactose monohydrate (Lact), polyvinyl-pyrrolidone K90 (PVP), colloidal silicon dioxide (col SiO2) and talcum.

3. For ***KET-FUM***, with the aim to develop a preparation method on a 1 g scale, within *A.1.6* activity the ***evaluation of the crystallization metastable zone width*** (MSZW) was performed.

4. For both co-crystals, in *A.1.5* activity, the acute ***in vivo*** **toxicity** was studied using Wistar rats. The acute toxicity test showed discrete hematologic and hepatic modifications, all of this modification being in agreement with the data reported in the literature for Ketoconazole, but at a lower level, which shows good biological tolerance for the investigated substances.

5. In *A.1.2* activity, the ***biocompatibility*** of KET-FUM and KET-PABA co-crystals was investigated on two human cell lines (dermal fibroblasts and endothelial cells). A decrease of the cell viability induced by KET-FUM and KET-PABA compared to KET was recorded.