

Characterization and stability of co-amorphous systems containing olanzapine and sulfonic acids

Inês A. Santos¹, Ana C. Bastos^{1,2}, João F. Pinto² and Ana I. Fernandes¹

¹CiiEM – Centro de Investigação Interdisciplinar Egas Moniz, Instituto Universitário Egas Moniz, Monte de Caparica, Portugal; ²iMed.Ulisboa – Research Institute for Medicines, Faculdade de Farmácia, Universidade de Lisboa, Lisboa, Portugal

aifernandes@egasmoniz.edu.pt

Introduction: A large number of active pharmaceutical compounds currently under development are poorly water soluble, which can limit their bioavailability and results in formulation challenges (1). Co-amorphous systems (CAMs) are known to increase the apparent solubility and dissolution rate of drugs (1, 2). To date, sulfonic acids have never investigated as possible co-formers for Olanzapine (OLZ; a BSC class II drug) and, thus, the aim of this work was to evaluate their potential on the formation of stable CAMs.

Materials and Methods: OLZ was used as model drug. Saccharin (SAC), cyclamic acid (CA), acesulfame (ACE; obtained by neutralization of potassium acesulfame) and their salts, sodium saccharin, sodium cyclamate and potassium acesulfame, respectively, were used as co-formers. Mixtures (2g) of OLZ and each co-former, in molar ratios 1:1, were submitted to milling, solvent evaporation (SE) and quench cooling. Samples were characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), Fourier-transform infrared spectroscopy (FTIR) and cooling/heating stage microscopy. Solubility assessment, powder dissolution rate and stability studies were also performed.

Results: SAC, CA and ACE demonstrated to be successful co-formers in the production and stabilization of OLZ-CAMs obtained by the three different techniques, presenting a single glass transition temperature (T_g) in thermograms and a typical halo in XRPD diffractograms. None of the salts were capable of forming a CAM, resulting in phase separation and absence of T_g events. Microscopical analysis supported DSC data and provided images of the CAMs recrystallization. Band shifts and broadening of the CAMs FTIR spectra suggest an intermolecular interaction between the N-H group in OLZ and the C=O group in SAC and ACE and the O-H group in CA. Solubility of OLZ was significantly increased (up to 199 times) when produced by SE with SAC. Dissolution rate was also increased for all the CAMs produced. SAC and CA successfully stabilized the CAMs produced, for more than 8 weeks at 25°C/11, 53 and 75% RH and at 25°C/11 and 53% RH, respectively.

Discussion and Conclusions: In this study OLZ was successfully amorphized using the neutral forms of the sulfonic acids. The impossibility of the salts to form a CAM is in agreement with the FTIR results, since the groups responsible for the molecular interaction with OLZ are unavailable in these molecules due to their negative charge. SE proved to be the best technique to produce CAMs with the different co-formers, resulting in the highest increase in solubility. SAC has shown to be the best co-former, with the highest solubility and stability over time, under higher relative humidity. Moreover, the increased dissolution rate of the CAMs suggests improved bioavailability of OLZ, a feature that should be confirmed *in vivo*.

References:

1. Blaabjerg LI, Lindenberg E, Rades T, Grohganz H, Löbmann K. Influence of preparation pathway on the glass forming ability. *Int J Pharm.* 2017;521:232-9.
2. Dengale SJ, Grohganz H, Rades T, Löbmann K. Recent advances in co-amorphous drug formulations. *Adv Drug Del Rev.* 2016;100:116-25.

Acknowledgements: Fundação para a Ciência e a Tecnologia (FCT) for financial support to this work (PTDC/CTM-BIO/3946/2014).