Comparison of the co-amorphization ability of olanzapine with amino, carboxylic and sulfonic acids

Ana C. Bastos[1,2], Nuno F. da Costa[1,2], Ana I. Fernandes[1], João F. Pinto[2]

[1] **CiiEM** – Centro de Investigação Interdisciplinar Egas Moniz, Instituto Universitário Egas Moniz, Monte de Caparica, Portugal

[2]**iMed.ULisboa** – Research Institute for Medicines, Faculdade de Farmácia, Universidade de Lisboa, Lisboa, Portugal

jfpinto@ff.ul.pt

INTRODUCTION

A large number of active pharmaceutical compounds currently under development are poorly water soluble, a characteristic which can limit their bioavailability and result in formulation challenges[1,2]. Strategies to address the problem encompass the conversion of a crystalline drug into an amorphous form to promote its apparent solubility and dissolution, thus resulting in a probable increase in bioavailability[3].

The production of co-amorphous systems has added value to the co-crystallization and amorphization of drugs by profiting from the advantages of both strategies to increase the apparent solubility of a drug. These systems incorporate low molecular mass molecules as co-formers, which are mixed with the drug at the molecular level to form one single co-amorphous phase[1-3].

The aim of this study is to understand the capability of different co-formers (amino, carboxylic and sulfonic acids), in the production of co-amorphous systems with olanzapine by ball milling, solvent evaporation and quench cooling of molten systems.

MATERIALS AND METHODS

Olanzapine (OLZ) was obtained from Vega Pharm (China), L-tryptophan (TRY) and L-proline (PRO) from BioChemica AppliChem (Spain); citric acid (CA), tartaric acid (TA), sodium saccharine (SAC) and solvents (ethanol and dichloromethane) from Sigma Aldrich (Germany); and liquid nitrogen from Air Liquide (Portugal).

Mixture – Mixtures of OLZ and each of the amino acids (TRY and PRO), carboxylic acids (CA and TA) or sulfonic acids (SAC) were obtained in a tumble mixer, in molar ratios 1:1, 1:2 and 2:1 prior to further processing.

Milling – 2g of particles in the previous mixture were continuously milled in a ball mill (Retsch, PM 100, Germany) with 3 mm balls, at 650 rpm, for 24 h.

Solvent evaporation - 2 g of the previous mixture was dissolved in 75 ml dichloromethane. The solvent was removed by evaporation at 40°C and reduced pressure; residual solvent was removed under vacuum, for 24 h.

Quench cooling – 2g of the mixtures of OLZ and each co-former were molten and then quench cooled (QC) in aluminium beakers. The temperature for each mixture was set at 220ºC to assure that all components have melted. Each sample was kept in the liquid state for 5 min to ensure complete melting with formation of a single liquid phase and then quenched cooled with liquid nitrogen.

Solubility assessment

Water suspensions of each sample were prepared and shaken continuously for 12 h. Once equilibrium was reached, samples of supernatant were filtered through 0.22µm PTFE filter and diluted to an appropriate concentration to allow quantification of OLZ by UV-Vis spectrophotometry (Shimadzu 2000, Japan) analysis (n=3).

Characterization of the samples

Samples were characterized by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier-transform infrared spectroscopy (FTIR). DSC studies of OLZ, binary co-amorphous mixtures were performed on samples weighing 3-5 mg in hermetic sealed crucibles (TA Instruments, Q200, USA). Samples were subjected to heating and cooling cycles at a rate of 10ºC/min, within the range of -40 to 250ºC.

X-ray diffraction (XRD) patterns were recorded in the transmission mode on a diffractometer (Philips Analytical PW 3050/60 X'Pert PRO, NL) equipped with a X'Celerator detector operating with monochromatized CuKα radiation in BraggBrentano geometry. The samples were gently consolidated in an aluminium holder and diffractograms were obtained by continuous scanning in a 2θ-range at 40kV and 30 mA from 5–35°.

Infrared spectra were recorded from all mixtures (FTIR spectrophotometer, ALPHA II, Bruker, Germany). Samples were placed directly on the crystal and spectra were collected over a range of 4000–525 cm^{-1} (12 scans per spectrum).

RESULTS AND DISCUSSION

Results have shown that OLZ could be converted into the amorphous state and produce co-amorphous systems. The quench cooling technique presented the most promising results whereas milling and solvent evaporation do not seem to be sufficient to produce co-amorphous systems with the blends drug:co-former, containing amino acids and carboxylic acids. On the other hand, the sulfonic acid (SAC) co-former presented the best results, since a co-amorphous system could be produced by all the techniques, in every molar ratio (Table 1).

Mixtures (1:1)	Ball Milling	Quench Cooling	Solvent Evaporation
OLZ:TRY	no	no	no
OLZ:PRO	no	yes	no
OLZ:CA	no	yes	no
OLZ:TA	no	yes	no
OLZ:SAC	yes	yes	yes

Table 1. Comparison of the capability of co-amorphization using different techniques and co-formers

Figure 1 represents the XRD pattern of OLZ:SAC (1:1) showing the typical halo (absence of crystalline peaks) suggesting the formation of a co-amorphous system.

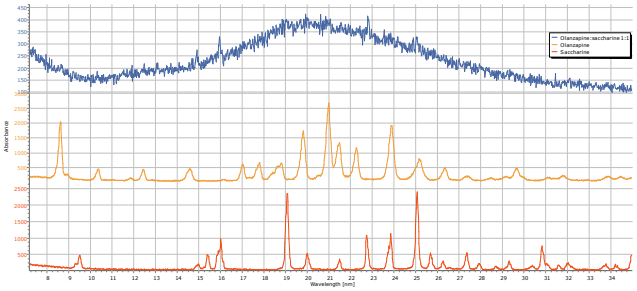

Figure 1. XPDR of OLZ:SAC (1:1) using solvent evaporation. – OLZ:SAC (1:1) – OLZ – SAC

Figure 2 presents the FTIR spectra of OLZ:SAC (1:1) which evidenced significant intermolecular interactions (hydrogen bonding) between N-H group in OLZ and the lactam C=O group in SAC, based on their characteristic shifts.

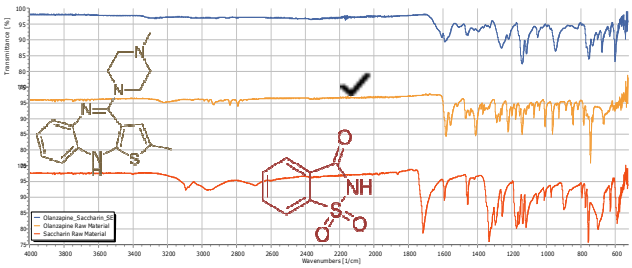

Figure 2. FTIR of OLZ:SAC (1:1) using solvent evaporation.

Figure 3 shows a set of thermograms for OLZ:SAC (1:1), OLZ and SAC and in the first thermogram a formation of a single glass transition (T_g=53.04ºC) is observed, suggesting the formation of a co-amorphous system.

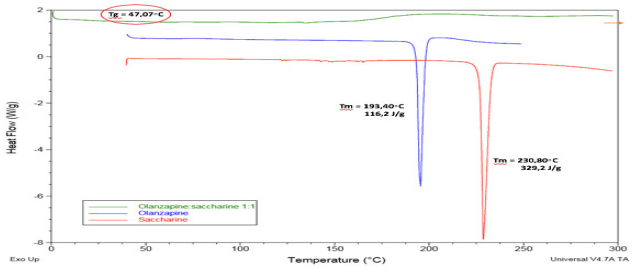

Figure 3. DSC of OLZ:SAC (1:1) using solvent evaporation. – OLZ:SAC (1:1) – OLZ – SAC

As a BCS class II drug, OLZ showed a low solubility in demineralized water (40 mg/L). The solubility of co-amorphous OLZ:SAC was much higher (SE=375x, BM=254x and QC=235x) than OLZ alone, or and in systems containing the other co-formers (around 30x for amino acids and 50x for carboxylic acids). The significant solubility improvement observed may increase dissolution *in vivo* and is likely to enhance bioavailability of OLZ.

CONCLUSION

The study has shown the possibility of converting OLZ into an amorphous entity, in the presence of co-formers, significantly promoting solubility.

Regarding the preparation method quench cooling was better than solvent evaporation and milling.

SAC, a sulfonic acid, was the best co-former probably because it is a stronger acid than amino or carboxylic acids, but also due to the conjugated ressonance aromatic ring promoting the establishment of hydrogen bonds with OLZ and amorphization.

ACKNOWLEDGEMENT

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

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