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Assessment of the stability of co-amorphous olanzapine in tablets

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ABSTRACT

Introduction: Amorphous and co-amorphous (CAM) materials have recently been used to improve oral bioavailability of drugs, by enhancing water solubility and dissolution rate from solid dosage forms [1,2]. However, stress conditions imposed on amorphous systems during production of such dosage forms (e.g. pressure upon tableting), can revert the drug back into the less soluble crystalline form [3]. This work thus presents a methodology to monitor and quantify the fraction of amorphous olanzapine (OLZ) remaining in immediate release OLZ tablets (Table 1).

Materials and methods: Near infra-red (NIR, 9000–4000 cm^{-1}) and Fourier-transform infra-red (FTIR, 4000–500 cm^{-1}) techniques were used to quantify the fraction of co-amorphous OLZ (30%) with saccharin (SAC; 18%) in formulations containing also calcium phosphate (27%), microcrystalline cellulose (20%) and povidone (5%). Tablets (250 mg) were obtained using a universal testing machine fit with circular punches (7.5 mm Ø), at a constant compression rate of 10 mm/min ($n = 5$); different compression forces (8 and 25 kN) and dwell times (DT; 0 and 20 min) were considered. Evaluation of the impact of the compression conditions on the recrystallization of OLZ from a co-amorphous system was based on a computational model.

Results: Using a 2nd derivative filter to process both NIR and FTIR spectra, the quantification of amorphous olanzapine was possible with a root mean square error of calibration and prediction above 2% (Figure 1). The method was further applied to evaluate the stability of co-amorphous systems after tableting, revealing that no significant recrystallization occurred, i.e. the co-amorphous were stable under the stress conditions applied.

Discussion and conclusions: The use of NIR and FTIR resulted in high correlation between the predicted values and the expected ones, thus enabling these spectroscopic techniques to be used to monitor the conversion of amorphous into crystalline OLZ forms and thus estimate the impact on drug bioavailability. Understanding of the conversion kinetics will ultimately allow anticipation of the time for complete recrystallization. The model developed has also demonstrated that tablets produced were stable, since no recrystallization was observed.

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Table 1. Predicted fraction of amorphous OLZ, by NIR and FTIR spectroscopies, in tablets prepared with the co-amorphous system.

ID	NIR	FTIR
CAM physical mixture	100	100
CAM 8 kN 0DT	89	98
CAM 8 kN 20DT	94	94
CAM 25 kN 0DT	95	93
CAM 25 kN 20DT	98	95

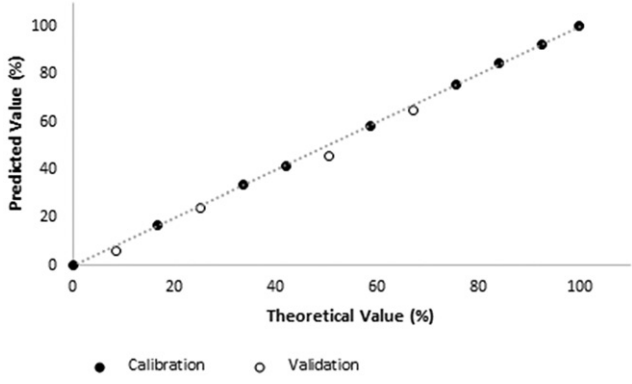

Figure 1. NIR calibration curve used to predict the amorphous fraction of OLZ..

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Characterisation and stability of co-amorphous systems containing olanzapine and sulphonic acids

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ABSTRACT

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, sulphonic acids have never investigated as possible co-formers for Olanzapine (OLZ; a BSC class II drug) and, thus, the aim of this work is 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 neutralisation of potassium acesulfame) and their salts, sodium saccharin, sodium cyclamate and potassium acesulfame, respectively, were used as co-formers. Mixtures (2 g) of OLZ and each co-former, in molar ratios 1:1, were submitted to milling, solvent evaporation (SE) and quench cooling. Samples were characterised by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD), Fourier-transform infra-red 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 stabilisation of OLZ-CAMs obtained by the three different techniques, presenting a single glass transition temperature (Tg) 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 Tg 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 stabilised 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 sulphonic 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 with therapeutic impact, which should be confirmed *in vivo*.

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