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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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Co-formability, solubility enhancement and stability of olanzapine co-amorphous systems produced with different co-formers

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ABSTRACT

Introduction: Strategies to address the problem of poorly water-soluble drugs encompass the conversion of a crystalline drug into an amorphous form to promote its apparent solubility and dissolution. Co-amorphous systems (CAMs) incorporate low molecular mass molecules (co-formers), which are mixed with the drug to form one single phase [1,2]. The aim of this study is to understand the capability of different co-formers (amino, carboxylic and sulphonic acids), in the production of CAMs with olanzapine by ball milling, solvent evaporation and quench cooling.

Materials and methods: Mixtures (2 g) of olanzapine (OLZ) and each co-former [L-aspartate (ASP); L-tryptophan (TRY); L-arginine (ARG); L-proline (PRO); citric acid (CIT); tartaric acid (TAR); oxalic acid (OXA); saccharine (SAC); potassium acessulfame (ACE); cyclamic acid (CYC)] in 1:1 molar ratios were submitted to ball milling (BM), solvent evaporation (SE) and quench cooling (QC). CAMs were evaluated for the OLZ solubility increase, co-formability and storage stability over time, by differential scanning calorimetry (DSC), X-ray powder diffraction (XRPD) and Fourier-transform infra-red spectroscopy (FTIR).

Results: The BM technique presented the most promising results followed by QC and SE (Table 1), since more CAMs were produced. All the sulphonic acids (SAC, CYC and ACE) formed CAMs regardless of the technique used, presenting complete amorphization probably due to their higher ability to produce intermolecular interactions, like hydrogen-bonding, thus increasing the stability of CAMs (more than 8 weeks at 25 °C/11 and 53% RH). Conversely, amino acids were the least efficient in producing CAMs. Crystalline OLZ presented low solubility (40.1 mg/L) in water and a general increase in the solubility of the CAMs was observed. Carboxylic acids (TAR, CIT, OXA) achieved the biggest increase (up to 269 times, BM with TART) followed by sulphonic acids (up to 199 times, SE with SAC), unveiling the possibility of improved dissolution profiles and bioavailability.

Discussion and conclusions: The study has shown the possibility of converting a crystalline drug into an amorphous entity, particularly when in presence of co-formers which stabilise the amorphous structures formed. In fact, with sulphonic acids, both SE and BM, achieved complete amorphization and successfully stabilised the CAMs obtained. Due to the noteworthy increase in solubility, resulting from co-amorphization, this technique is considered to be adequate to process active compounds with poor water solubility, such as OLZ.

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

Mixtures	QC	SE	BM
OLZ:PRO	Yes[a]	No	No
OLZ:ARG	No	No	No
OLZ:TRY	No	No	Yes[a]
OLZ:SER	No	No	No
OLZ:ASP	No	No	Yes[a]
OLZ:CIT	Yes[a]	No	Yes[b]
OLZ:TAR	Yes[a]	No	Yes[b]
OLZ:OXA	Yes[a]	No	No
OLZ:SAC	Yes[b]	Yes[b]	Yes[b]
OLZ:CYC	No	Yes[b]	Yes[b]
OLZ:ACE	Yes[b]	Yes[b]	Yes[b]

[a]Incomplete amorphization; [b]complete amorphization.