In-situ co-amorphization of olanzapine in pellets

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INTRODUCTION

Approximately 70-90% of the new chemical entities in the discovery and development pipelines present poor aqueous solubility, impacting negatively on their bioavailability[1]. Co-amorphization of drugs has been described as a promising strategy to enhance the solubility and dissolution properties of drugs[2]. However, co-amorphous systems when submitted to stress conditions (e.g. heat or moisture) are likely to have their recrystallization rate increased, thus reducing the solubility and dissolution advantages[3]. Thus, strategies to increase the stability of co-amorphous materials, particularly in drug products, must be developed.

This work aimed at the *in situ* co-amorphization of olanzapine (OLZ) while coating nonpareil beads (placebo) to simultaneously enhance the dissolution rate and reduce the recrystallization of the amorphous drug.

MATERIALS AND METHODS

To produce the co-amorphous system, OLZ (Rampex Labs Pvt. Ltd, India), used as a BCS class II model drug, and saccharin (SAC) (Sigma-Aldrich, Steinheim, Germany), in a 1:1 molar ratio, were dissolved in dichloromethane (Biochem Chemopharma, France) prior to evaporation of the solvent at 650 mbar/40°C using a Buchi Rotavapor (R-100, Switzerland).

Preparation of pellets

Placebo pellets were made of anhydrous dibasic calcium phosphate (75%, Budenheim, Germany), microcrystalline cellulose (20%, FMC Corp., Ireland), and povidone (5%, BASF, Germany). Powders were dry blended prior to wetting with water (30%, dry basis). After storage for 24 h, the wet mass was extruded with a ram extruder fixed to a universal testing machine (Lloyd Instruments, Florida, USA) and extrudates spheronized for 10 min (Caleva, UK). Solutions of OLZ (5%), with, or without, SAC (3%), in dichloromethane were prepared and used to coat the pellets in a fluidized bed equipment (Aeromatic Fluid Bed Dryer, Niro Inc., USA) prior to drying at 40°C, until constant mass.

Uncoated pellets containing OLZ (5%) were obtained after dry blending a powder mixture made of anhydrous dibasic calcium phosphate (71%), microcrystalline cellulose (19%) and povidone (5%) and pelletized as described previously. When SAC (3%) was added to the powdered mixture, a proportional reduction in the fraction of the other excipients was considered.

Characterization of samples

X-ray powder diffraction (XRPD) was performed in an X-ray diffractometer (PANalytical, The Netherlands) with a CuKα source of radiation (λ=1.54 Å) set at 40kV and 30 mA. A step size of 0.017°2θ was considered, within the range 7 to 35 °2θ, and at a counting time of 19.685 s.

Fourier-transformed mid infrared spectra (FTIR) were acquired (4,000–525 cm^{-1}, at a resolution of 4 cm^{-1}, n=5) with a spectrophotometer (Bruker, USA) connected to a diamond attenuated total reflectance accessory (Bruker, USA).

Near-infrared spectra (NIR) were obtained (10,000-4,000 cm^{-1}, at a resolution of 8 cm^{-1}, n=5) with a spectrophotometer (ABB, Canada) coupled to an indium-gallium-arsenide detector and considering polytetrafluoroethylene as background (ABB, Canada). Samples were placed in borosilicate flasks and scanned 32 times to produce an averaged absorbance spectrum (n=5). The spectral data collected was analyzed using the Spectagryph software (v 1.2.13, 2019, Germany).

Principal component analysis (PCA) was applied to the FTIR and NIR spectra to evaluate their similarity (Matlab software, R2015a, 2015, MathWorks, USA).

Dissolution experiments were conducted on pellets (200mg, i.e., 10 mg of OLZ, n = 3) in a dissolution apparatus (paddle method, 100 rpm, Sotax, Switzerland) containing phosphate buffer (pH 6.8, 37±0.5°C, 1000 mL). At predefined time points, samples were collected and filtered through a 0.22 μm MCE filter and analyzed by UV spectrophotometry (λ= 254 nm, Hitachi, Japan).

Drug content uniformity was determined by dissolving (approximately 200 mg of pellets, gently milled with a mortar and pestle), in 1000 mL of deionized water (n=10). OLZ was quantified by UV spectrophotometry, as described previously.

RESULTS AND DISCUSSION

Co-amorphization of OLZ was described previously as a method to enhance the water kinetic solubility and dissolution rate of the drug[3]. Diffractograms of co-amorphous OLZ samples presented the typical halo pattern and the absence of crystalline peaks, suggesting the complete amorphization of both OLZ and SAC. The stability of the co-

amorphous system throughout the production of pellets was evidenced since diffractograms of extrudates and pellets have not shown any signs of recrystallization of the drug (e.g., presence of crystalline peaks). Interestingly, the coating of the placebo pellets resulted in samples in which the diffractograms suggested the amorphization of OLZ and SAC, confirming the feasibility of the strategy to prepare co-amorphous systems, without the need of prior production of those systems to manufacture drug products. Inversely, the drug crystallinity was maintained when OLZ, in the absence of SAC, was present either in the core or in the coating layer of the pellets. The presence of co-amorphous OLZ on the surface of pellets was ascertained by FTIR and NIR spectroscopy. The co-amorphization of OLZ and SAC is accomplished by the establishment of interactions between the compounds, as reflected by the spectral differences, reflecting minor changes in the amorphous/crystalline contents in samples[3]. Spectra of pellets coated with OLZ-SAC were similar to those of samples containing the co-amorphous OLZ previously prepared by solvent evaporation. These results confirm the co-amorphization of OLZ during the process of coating and the stability of such systems throughout the coating process.

Dissolution studies were then performed to assess the release of OLZ from pellets (Figure 1). Significant differences were found at early stages of the dissolution test, namely when OLZ was present in the core of pellets (t_{50}=119 min) and OLZ and SAC were present in the coat (t_{50}=4 min). Similarly, higher dissolution rates were observed for pellets containing OLZ-SAC in the coat (highest dissolution rates observed) than in the core.

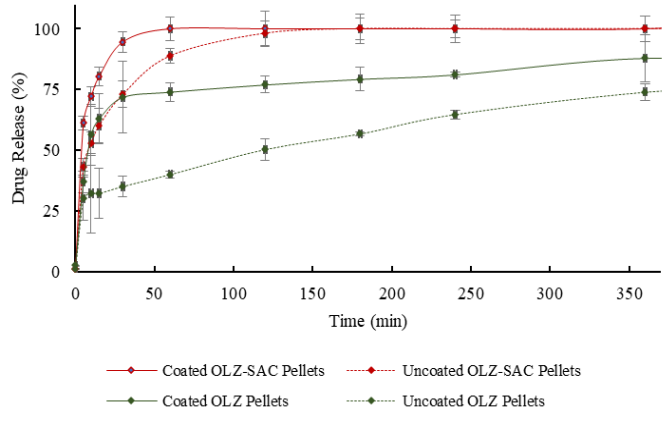

Figure 1: Dissolution profiles of coated and uncoated pellets with OLZ and with OLZ-SAC

The presence of OLZ in the coat made it available for immediate release (particularly in the presence of SAC) by opposition to OLZ present in the core, which release was hampered by the matrix like structure of the pellets. Worth to point out that at the end of the dissolution studies (24 h) all OLZ was released and dissolved in the phosphate buffer (under sink conditions).

Content uniformity studies confirmed the target drug load (5%).

CONCLUSION

The feasibility of coating placebo pellets as a novel method to prepare *in situ* co-amorphous systems was proved in this work. Co-amorphization of OLZ in the coat of the pellets makes the pre-production of the co-amorphous systems, prior to the manufacture of drug products, unnecessary without affecting the stability of the co-amorphous system.

The results also highlighted the positive impact on the release of OLZ when it is present in an amorphous form, on the surface of pellets. As anticipated, an enhanced dissolution rate was obtained upon the coating of pellets, compared to those where the co-amorphous entity was present in the core of the pellets.

This work demonstrated the feasibility of using a coating process to generate dosage forms (e.g. pellets/tablets) as carriers of co-amorphous systems of poorly water soluble drugs.

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