Downstream processing of co-amorphous olanzapine

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INTRODUCTION

Co-amorphization of poorly water-soluble drugs has been shown to promote significant increases on solubility, dissolution rate and bioavailability [1]. While the preparation of co-amorphous entities is well described in literature, the processability of these entities in the manufacture of final dosage forms is still in its early stage. Measurements of flowability and compressibility related attributes are critical to ensure the manufacturability of formulations [2]. The measurement of the flowability of mixtures can be used to anticipate the successful filling of the die cavities of the compression machine and thus influence the quality attributes of drug products (such as weight and dosage uniformity) [3]. Contrarily, compressibility represents the capability of a powder bed to reduce its volume due to the application of compression pressures, and can be related with the flowability of mixtures [4].

The work developed aimed at the evaluation of the feasibility of co-amorphous olanzapine in the fabrication of tablets. For that, the flowability (e.g. angle of repose) and compressibility properties (e.g. Carr index), of this material were measured and compared to those of its crystalline counterparts.

MATERIALS AND METHODS

Olanzapine (a gift from Rampex Labs Pvt. Ltd, Telangana, India) was used as model drug. Olanzapine is an antipsychotic BCS class II drug which presents a water solubility of 43 mg/L and a bioavailability of 60%. Co-amorphization of olanzapine was accomplished with saccharin (Sigma-Aldrich, Steinheim, Germany) as co-former using the solvent evaporation preparation technique (R-100, Buchi Rotavapor, Flawil, Switzerland). Dichloromethane used as solvent (Biochem Chemopharma, Cosne sur Loire, France) and evaporated at 650 mbar/45°C.

Evaluation of co-amorphous olanzapine

X-ray powder diffraction (XRPD) and differential scanning calorimetry (DSC) were used to confirm the preparation of the co-amorphous containing olanzapine. A X-ray diffractometer (X'Pert PRO, PANalytical, Almelo, the Netherlands) with a CuKα source of radiation (λ=1.54 Å) set at 40kV and 30 mA with a step size of 0.017°2θ, within the range 7 to 35 °2θ, and a counting time of 19.685 s. Thermal analysis was performed using a TA calorimeter (Q200, TA Instruments, New Castle, USA). 5 mg of each sample were weighted and introduced in hermetically sealed aluminum pans prior to analysis in the modulated mode from -40 to 240°C. The analysis was carried out under a nitrogen gas flow of 50 mL/min, at a heating rate of 2°C/min and an amplitude of 0.318°C, for a period of 60s. Prior to the characterization, the powdered samples were gently milled, using a mortar and pestle, and passed through a 355µm mesh to ensure a uniform particle size.

Rheological characterization

Powder Rheology: Powder flow measurements (n=3) were performed using a TA.XT Plus Texture Analyzer fit with a powder flow device (TA.XT Plus, Stable Micro Systems, Surrey, United Kingdom). A sample of 30 g was placed in the glass sample holder (120 mm height and 50 mm internal diameter) to evaluate the cohesiveness and caking properties. Cohesion index was determined by dividing the work required to move up the blade (75 mm/s) by the weight of the sample. For the caking measurements, 5 compaction cycles were imposed to samples (500 g). After the 5 cycles, the blade overpassed the produced cake and the hardness required to break up the cake was recorded (caking strength).

Angle of Repose: Samples with 20 g were placed into a funnel (Ø=13 mm)and the test protocol was performed according to the Ph. Eur.[5]. The discharge of the samples trough the funnel resulted in the formation of a powder cone in the circular plate. The angle of repose was calculated by measuring the diameter and the height of the cone.

Bulk and Tap Density: A 50 cm^3 cylinder was filled with the samples and the bulk density was determined. Then, the cylinder was accoupled to the tap density apparatus (Stampfvolumeter STAV 2003, Jel, Ludwigshafen am Rhein, Germany). After 1250 taps the tapped volume of the sample was stabilized and thus it was measured in order to determine the tapped density (n=3). Based on these the Carr Index and the Hausner ratio were determined.

	Angle of Repose (°)	Cohesion Index	Caking Strength (g)	Carr Index	Hausner Ratio
Crystalline	50.97 ± 0.89	1.30 ± 0.06	159.62 ± 6.88	35.516 ± 0.172	1.551 ± 0.004
Co-Amorphous	54.60 ± 1.72	2.48 ± 0.15	171.82 ± 5.93	36.663 ± 0.630	1.579 ± 0.016

Table 1- Rheological characterization of crystalline and co-amorphous olanzapine and saccharin.

RESULTS AND DISCUSSION

The XRPD diffractograms (Figure 1A) have shown the presence of a halo pattern and the absence of crystalline peaks in the product suggesting the full amorphization of both olanzapine and saccharine. Complementary, DSC thermograms (Figure 1B) have shown a unique T_g at 57°C and the absence of melting events supporting the amorphization of both OLZ and SAC and the likely miscibility of these compounds.

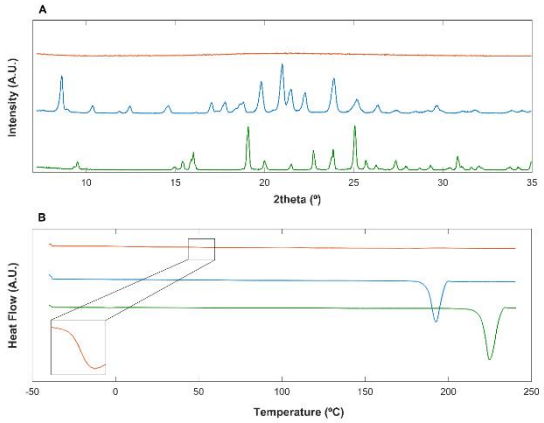

Figure 1- XRPD diffractograms (A) and DSC thermograms (B) of co-amorphous OLZ (in orange), pure crystalline OLZ (in blue) and pure crystalline SAC (in green).

The angle of repose measurements have shown that co-amorphous olanzapine revealed a higher value than its crystalline counterpart (Table 1) anticipating problems of flow of the amorphous materials. Herewith it is important to remark that particle size of all samples was kept constant to minimize its effect on powder flowability. These results can be possibly explained due to the higher cohesiveness and caking tendency of co-amorphous olanzapine compared to the physical mixture crystalline materials (Table 1). This caking enhancement permits to anticipate the superior agglomeration of powders during storage and transportation.

Carr Index and Hausner Ratio suggest a higher compressibility than its crystalline counterpart (Table 1) with a higher consolidation forces between particles, which can be advantageous in tablet manufacturing due to the expected high capacity of volume reduction to be achieved. Carr index and Hausner ratio were in agreement with the angle of repose and cohesiveness results regarding the high cohesiveness of blends, as anticipated.

CONCLUSION

Co-amorphization of olanzapine and saccharin has shown to result in the production of a high cohesive powder and demonstrating poor flow properties. Thus, increased difficulties are expected to occur as result of the utilization of co-amorphous olanzapine in the manufacture of oral dosage forms.

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