Solid state conversion of olanzapine during tableting

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INTRODUCTION

The production of amorphous and co-amorphous materials has been used as a pathway to address the poor water solubility presented by the synthetic, more complex and hydrophobic drug substances (Mizoguchi et al., 2019). The preparation of amorphous systems can be accomplished by the application of various techniques such as milling, quench cooling or spray drying (Nair et al., 2019). However, limited studies have been conducted regarding the stability of amorphous and co-amorphous materials used for the production of dosage forms intended for oral administration (Chavan et al., 2016; Dengale et al., 2016).

The present work evaluates tableting as an additional method to produce the amorphous form of drugs. The forces/energy applied during tableting of a mixture composed of crystalline olanzapine, a BCS class II drug used as a model, were investigated as promoters of the dry solid-state amorphization of drugs for water solubility enhancement.

MATERIALS AND METHODS

Olanzapine (30%, OLZ) was a generous gift of Rampex Labs Pvt. Ltd (Telangana, India) and saccharin (18%, SAC) was purchased from Sigma-Aldrich (Steinheim, Germany). OLZ tablets formulation also contained dibasic calcium phosphate anhydrous (27%, DCPA, a gift from Budenheim, (Budenheim, Germany), microcrystalline cellulose (20%, MCC, Avicel PH-101, FMC Corp., Cork, Ireland) and povidone (5%, PVP K25, BASF, Ludwigshafen, Germany).

Preparation of Tablets

300 mg of powder mixture were directly compacted using a Lloyd Instruments LR50k Plus testing machine (Florida, USA). The equipment was fitted with Ø 7.5 mm flat punches and compressed at a rate of 10 mm/min until a predefined compression pressure (45, 160 and 270 MPa) was achieved. At that stage, tablets were (1) immediately ejected or (2) further compressed for 5 minutes at the defined compression pressure.

Characterization of Tablets

The physical mixtures and the tablets produced were characterized by X-ray powder diffraction (XRPD), Fourier-transform near- and mid-infrared spectroscopy (NIR and FTIR respectively) to monitor the fraction of co-amorphous OLZ at each time of the process (Savolainen et al., 2007).

XRPD was performed using an X'Pert PRO X-ray diffractometer (PANalytical, Almelo, the Netherlands) using a CuKα (λ=1.54 Å) source of radiation and with a defined voltage and current of 40kV and 30mA, respectively. The samples were analyzed using a step size of 0.017 °2θ with a counting time of 19.685 s in the range 7-35 °2θ.

FTIR spectra were obtained with a spectrophotometer (Alpha II FTIR Spectrometer, Bruker, Germany) connected to an attenuated total reflectance accessory (Platinum ATR, Bruker, Germany). Samples were scanned over the wave number range 4000-525cm^{-1} at a defined resolution of 4cm^{-1}.

NIR spectra were obtained with a spectrophotometer (TLA 2000, ABB, Québec, Canada) fitted with an indium-gallium-arsenide detector and considering PTFE (polytetrafluoroethylene) as background (SKG8613G, ABB, Québec, Canada). Samples, in triplicate, were placed in borosilicate flasks and scanned for 32 times over a wavenumber range from 10,000 to 4,000 cm^{-1} (resolution of 8 cm^{-1}).

RESULTS AND DISCUSSION

The regression methods developed with NIR, FTIR and XRPD data have shown to be able to predict the fraction of co-amorphous olanzapine. The small error associated with the prediction of the points used to calibrate and validate the regression methods enabled its application for the prediction of the amorphization and/or recrystallization behaviour of amorphous dispersions during tableting (Table 1 and Figure 1).

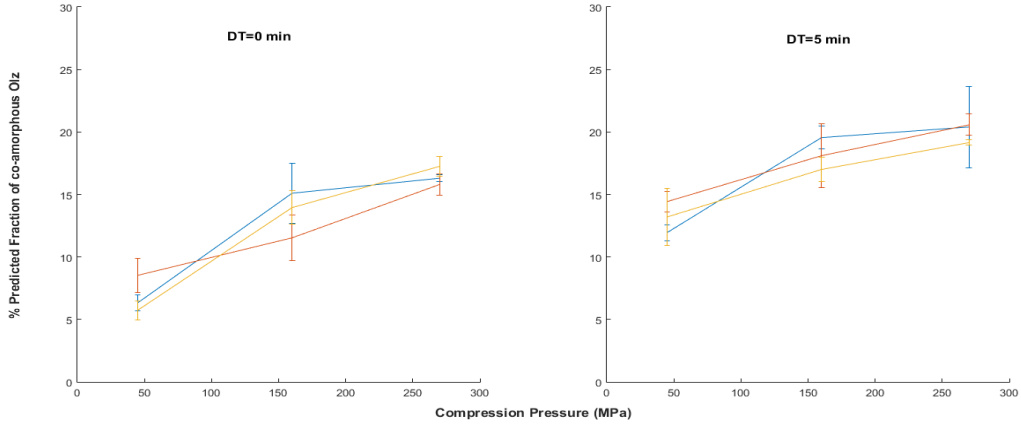

Figure 2- Influence of the compression pressures and dwell times in the co-amorphous fraction of OLZ according to the predictions performed with NIR (blue), FTIR (orange) and XRPD (yellow).

RMSE (%)	NIR	FTIR	XRPD
Calibration	1.9	2.6	2.9
Prediction	1.5	3.1	4.4

Table 1- Root mean square error (RMSE) for the methods developed with NIR, FTIR and XRPD analysis.

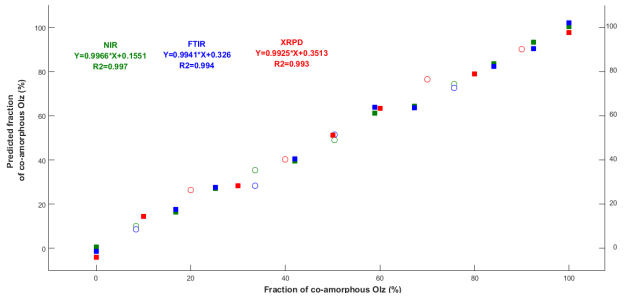

Figure 1- Regression methods developed with the NIR (blue), FTIR (red) and XRPD (green) data [Squares represent the calibration whilst circles represent the validation points].

The application of high energies to the mixtures during tableting was responsible for a partial co-amorphization of OLZ. The co-amorphization was especially relevant during the application of compression pressures up to 160 MPa. For compression pressures higher than 160 MPa stabilization of the co-amorphous OLZ fraction of was observed (Figure 2).

CONCLUSIONS

The production of amorphous and co-amorphous entities is used to overcome drug solubility issues. The work here described has shown that tableting is a suitable technique to produce co-amorphous entities. It was also demonstrated that both an increase in the compression pressure and in dwell time were responsible for an increase in the co-amorphous fraction of OLZ. Thus, tableting can be regarded as an advantageous approach for simultaneous production of oral solid dosage forms and the co-amorphization of poorly water soluble drugs.

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