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 [1]. The preparation of amorphous systems can be accomplished by the application of various techniques such as milling, quench cooling or spray drying [2,3]. Thus, prior to the manufacture of pharmaceutical drug products, amorphous or co-amorphous should be prepared, which may result in stability concerns and high manufacturing costs.

The present work evaluates tableting as an additional method to produce the amorphous form of drugs, and thus reducing the risk of recrystallization prior or during the production of tablets. The energy applied during tableting of a mixture containing crystalline olanzapine (OLZ), a BCS class II drug used as a model, was investigated as promoter of the dry solid-state amorphization of the drug for water solubility enhancement.

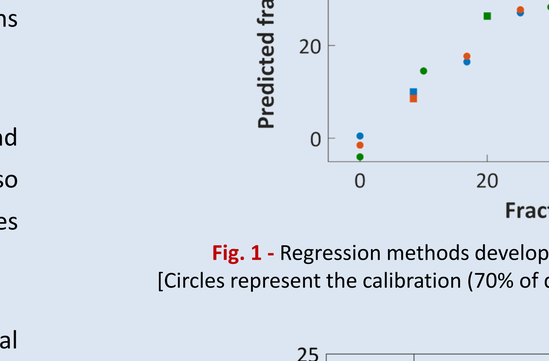
Materials and Methods

Olanzapine (OLZ; 30%)

+

Saccharin (SAC; 18%)

Dibasic calcium phosphate anhydrous (27%)
+
Microcrystalline Cellulose (20%)
+
Povidone (5%)



Characterization techniques: NIR, FTIR, XRPD

Compression Pressure: 25, 90 and 155 MPa
Dwell Time: 0, 2 and 5 minutes

Results and Discussion

X-ray powder diffraction (XRPD) and Fourier-transform near- and mid-infrared spectroscopy (NIR and FTIR, respectively) were used to monitor the fraction of co-amorphous OLZ.

Regression models were constructed considering the information provided by these techniques. The models could effectively predict the fraction of co-amorphous OLZ in samples, as ascertained by the linearity of the equations which describe them (Fig. 1). Moreover, the small root mean square errors associated with the prediction of the points used to calibrate (2.9, 1.9 and 2.6 for XRPD, NIR and FTIR respectively) and validate the regression methods (4.4, 1.5 and 3.1 for XRPD, NIR and FTIR respectively) showed the accuracy of the method and enabled its application for the prediction of the amorphization and/or recrystallization behaviour of amorphous dispersions during tableting.

The models developed suggested that the co-amorphous OLZ entities prepared beforehand remain stable after tableting, at different compression pressures and dwell times. Results also demonstrate the applicability of the models to monitor the stability of co-amorphous entities during the manufacture of tablets.

Interestingly, direct compaction of the formulation containing the crystalline OLZ:SAC physical mixture achieved a significant degree of amorphization upon pressure application (up to 20% under the conditions used). The partial co-amorphization of OLZ was especially relevant during the application of compression pressures up to 155 MPa. In this range, the higher compression pressure and the dwell time, the higher the extent of amorphization achieved (Fig. 2). For compression pressures higher than 155 MPa stabilization of the co-amorphous OLZ fraction of was observed (data not shown).

Results seem to indicate that the energy applied during compaction can lead to the amorphization of the drug. Tableting may be used as an alternative method to prepare amorphous dispersions, with the advantage of precluding the prior production of the co-amorphous systems, which have been shown elsewhere (see poster “Downstream processing of co-amorphous olanzapine”) to exhibit poorer bulk flow properties than the crystalline counterparts.

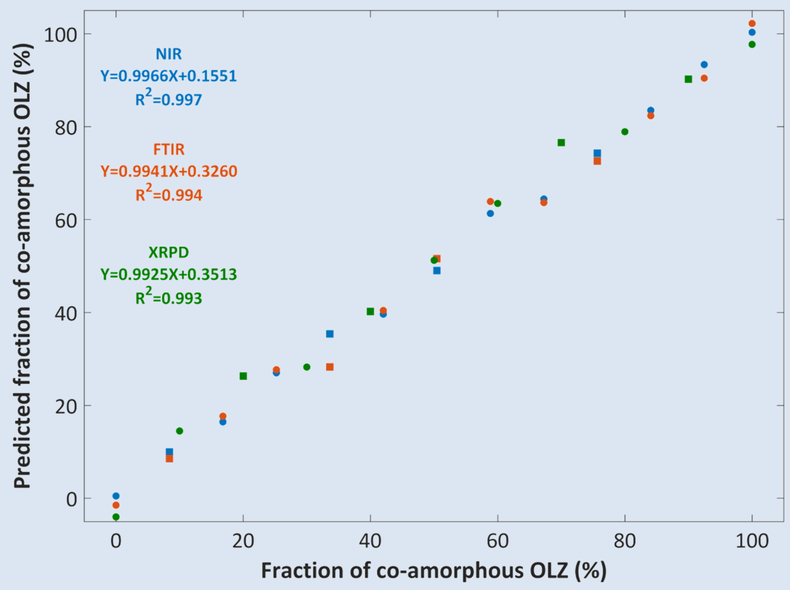


Fig. 1 - Regression methods developed with the NIR (blue), FTIR (orange) and XRPD (green) data.
[Circles represent the calibration (70% of data), whilst squares represent the validation points (30% of data)]

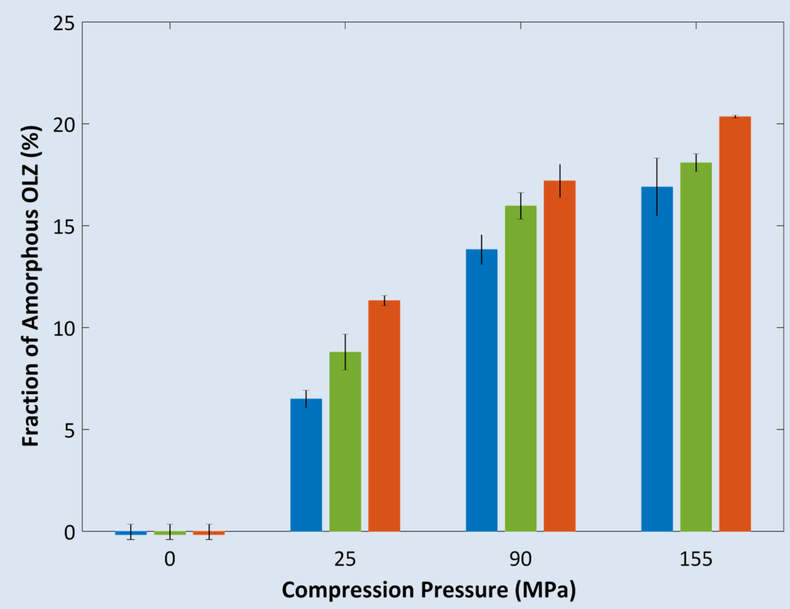


Fig. 2 – Effect of compression pressure and dwell time in the amorphization extent of OLZ.
[blue: 0 min, green: 2 min and orange: 5 min]

Conclusions

- The regression methods developed with NIR, FTIR and XRPD data are linear and accurate and shown to be able to predict the fraction of co-amorphous OLZ; these find application to monitor crystal/amorphous fractions during tableting and stability over time;
- Tableting is a suitable technique to produce co-amorphous entities due to the application of high energy in the process; both an increase in the compression pressure and in dwell time were responsible for an increase in the co-amorphous fraction of OLZ.
- Tableting can thus be regarded as an advantageous expedite approach for the simultaneous production of oral solid dosage forms and co-amorphization of poorly water-soluble drugs.

References

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