

INTRODUCTION

Amorphous and co-amorphous (CAM) materials have been used in the last years as a strategy to overcome the low bioavailability of the majority (90%) of drugs due to low water solubility and low dissolution rates from solid dosage forms (1,2). Unit operations used to produce oral solid dosage forms impose stress conditions (e.g. pressure during tableting) on amorphous systems and can promote the recrystallization of the amorphous drug (3).

This work presents new usages of spectroscopic based analytical methods and computational models to quantify the fraction of amorphous olanzapine (OLZ) in a formulation intended to produce immediate release OLZ tablets.

MATERIALS AND METHODS

Near infrared (NIR) and Fourier-transform mid infrared (FTIR) spectroscopies were used to quantify the fraction of co-amorphous OLZ (30%) with saccharin (SAC; 18%) in formulations containing also calcium phosphate (27%), microcrystalline cellulose (20%) and povidone (5%).

Tablets (250mg) were obtained using a universal testing machine fit with circular punches (7.5mm \varnothing), at a constant compression rate of 10mm/min (n=5). Different compression forces (8 and 25kN) and dwell times (DT; 0 and 20 min) were considered to produce tablets. Evaluation of the impact of the compression conditions on the recrystallization of OLZ from a co-amorphous system was based on a computational model.

RESULTS AND DISCUSSION

Using a 2nd derivative filter to process both NIR and FTIR spectra, the quantification of amorphous olanzapine was possible with a root mean square error of calibration and prediction above 2% (Fig. 1).

For near infrared spectroscopy, the wavenumbers between 5660 and 5620 cm^{-1} have shown a strong correlation with the fraction of amorphous olanzapine present in each sample point. Considering this region, a calibration curve with a R^2 of 0,9999 was obtained, which justifies the use of this method to assess the amount of amorphous olanzapine, and thus to predict the drug's expected bioavailability.

For mid infrared spectroscopy, the wavenumbers between 2820 and 2770 cm^{-1} were found to be the most significant to predict the amorphous fraction of olanzapine. Using these wavenumbers a regression curve with a R^2 of 0,998 was obtained, although the error associated with the prediction of external samples was higher than the one obtained with near infrared spectroscopy.

The method was further applied to evaluate the stability of co-amorphous systems after tableting, revealing that no significant recrystallization occurred, i.e. the co-amorphous were stable under the stress conditions applied.

Table 1. Predicted fraction of amorphous OLZ by NIR and FTIR spectroscopy, in tablets prepared with the co-amorphous system

ID	NIR	FTIR
CAM Physical Mixture	100	100
CAM 8kN ODT	89	98
CAM 8kN 20DT	94	94
CAM 25kN ODT	95	93
CAM 25kN 20DT	98	95

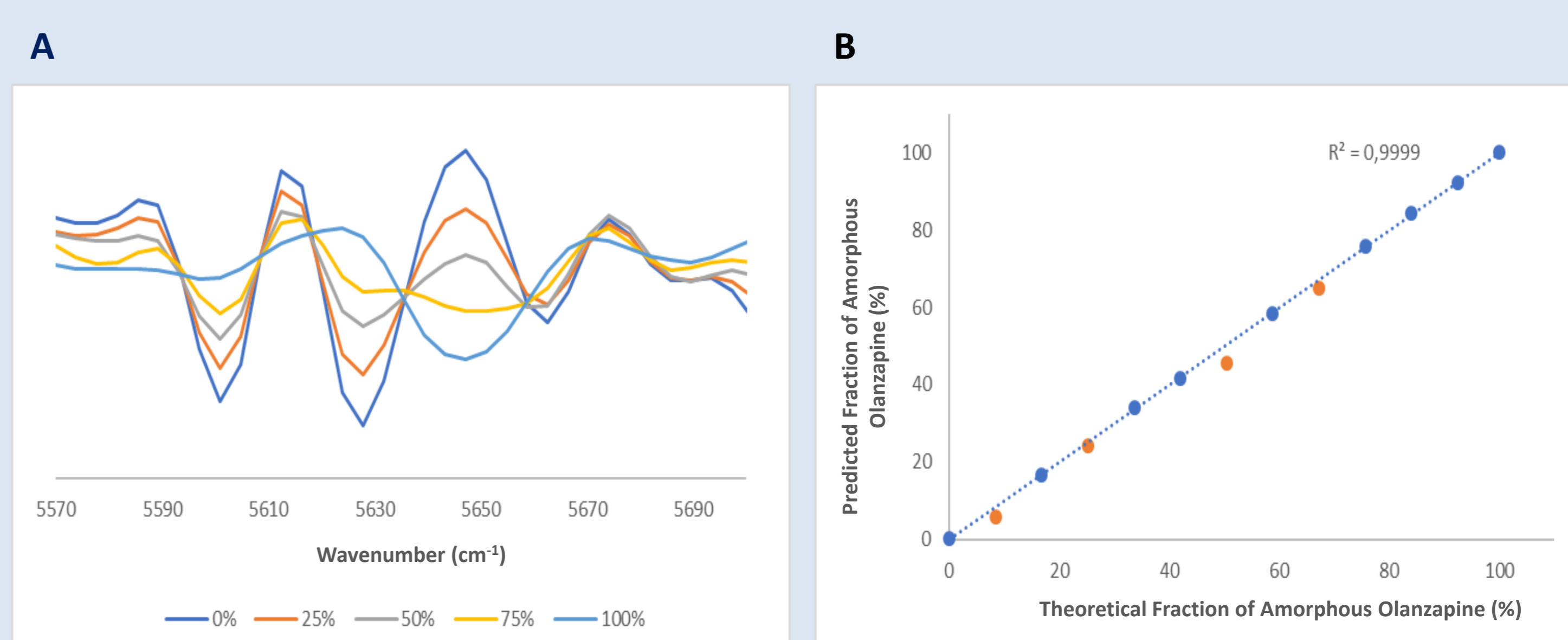


Fig. 1. 2nd derivative NIR (coloured according to the fraction of amorphous olanzapine) of the selected wavenumbers used to develop the computational method (A). Comparison between the theoretical value and the predicted fraction of amorphous olanzapine obtained using the computational method (B; in blue points used to calibrate the model and in orange the samples used to validate it).

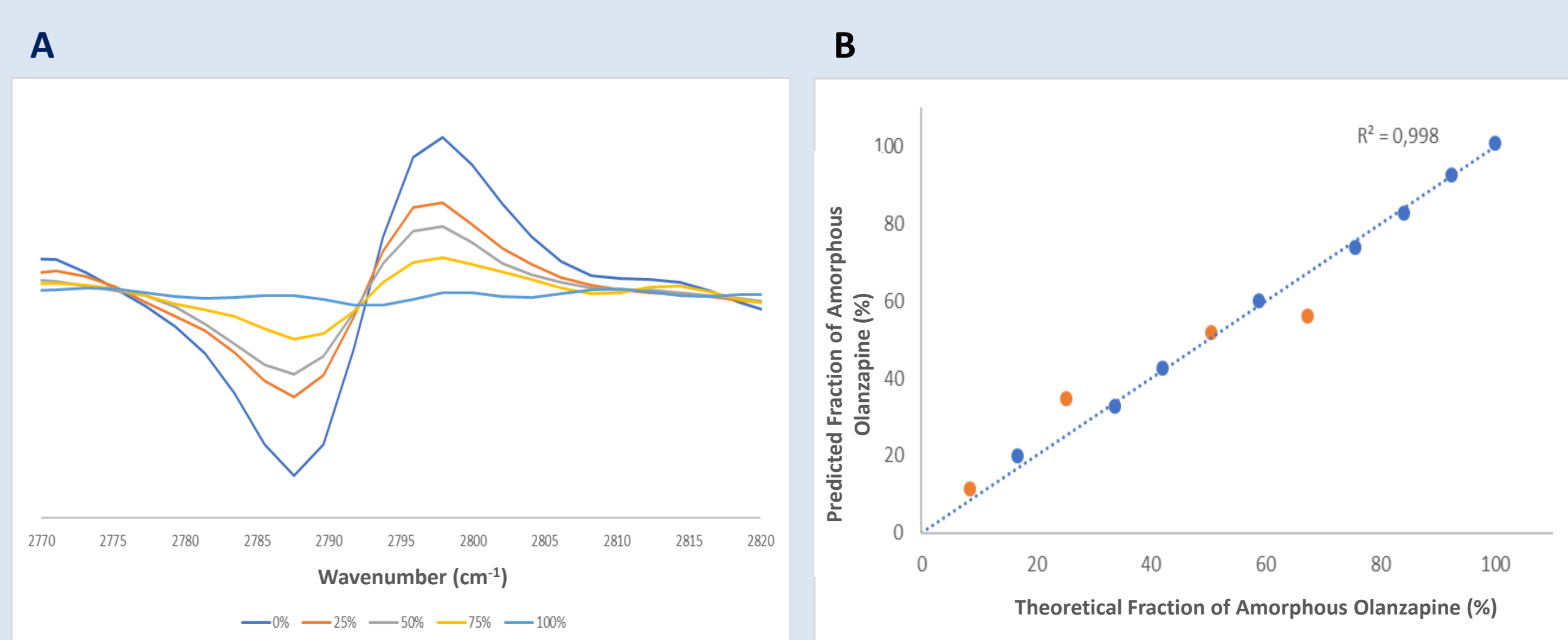


Fig. 2. 2nd derivative mid infrared spectra (coloured according to the fraction of amorphous olanzapine) of the selected wavenumbers used to develop the computational method (A). Comparison between the theoretical value and the predicted fraction of amorphous olanzapine obtained using the computational method (B, in blue points used to calibrate the model and in orange the samples used to validate it).

CONCLUSIONS

Using both NIR and FTIR spectroscopy it was possible to develop a methodology to monitor and quantify the conversion of the amorphous OLZ present in blends as a co-amorphous of OLZ:SAC. The models developed have also demonstrated that all tablets obtained were stable with the application of different compression pressures and dwell times, since no recrystallization was observed.

REFERENCES

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