Development of an at-line method to monitor the conversion of amorphous into crystalline olanzapine, in dry blends or wet masses

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Framework

Currently, more than 70% of drugs under R&D show extremely low solubility in water, which ultimately compromise their bioavailability [1]. To minimize this problem several techniques have been considered in the last years, namely the production of solvates, polymorphs or eutectic mixtures. Among these techniques, the production of amorphous materials has been established as one of the most promising approaches to enhance drugs' solubility. Despite the large increase in solubility presented by the material in the amorphous state, they are highly instable, thus preventing their utilization in the pharmaceutical industry due to short and unpredictable stability, prior to conversion into a more stable state [2-4]. Co-amorphous systems have been studied for the last 10 years as an alternative strategy to delay and prevent the recrystallization of the drug. Co-amorphous are mixtures of a drug molecule and a co-former which can be either a second drug or a low molecular weight excipient. The potential establishment of bonds between compounds is expected to promote the stability of the composite material. The choice between the formation of an amorphous or a co-amorphous system depends on the drug and its therapeutic use. The present work aimed at the development of a monitoring strategy to evaluate the recrystallization of the co-amorphous olanzapine (OLZ), a BCS class II drug, and saccharin (SAC).

Methodology

A mixture comprising olanzapine and saccharin in a 1:1 molar ratio was dissolved in dichloromethane and co-amorphization was carried out by evaporation of the solvent. The product obtained was characterized by differential scanning calorimetry (DSC) and X-ray powder diffraction (XRPD) to ascertain the production of a co-amorphous entity.

Different amounts of the OLZ:SAC co-amorphous powder (0-15.6%) were blended with anhydrous dibasic calcium phosphate (59.4%), microcrystalline cellulose (20.0%) and povidone (5.0%). The fraction of OLZ:SAC in the formulation was kept constant by the addition of crystalline OLZ (0-10.0%) and SAC (0-5.8%). Additionally, different fractions of water were added to the final mixtures immediately before the analysis of the wet masses.

Near infrared spectroscopy (NIR) and Fourier Transform infrared spectroscopy (FTIR) were considered to evaluate spectral differences between the various formulations containing different fractions of amorphous olanzapine. Approximately 70% of the sample points were randomly selected to calibrate the model and the remaining 30% were used to validate the model proposed.

Results and Discussion

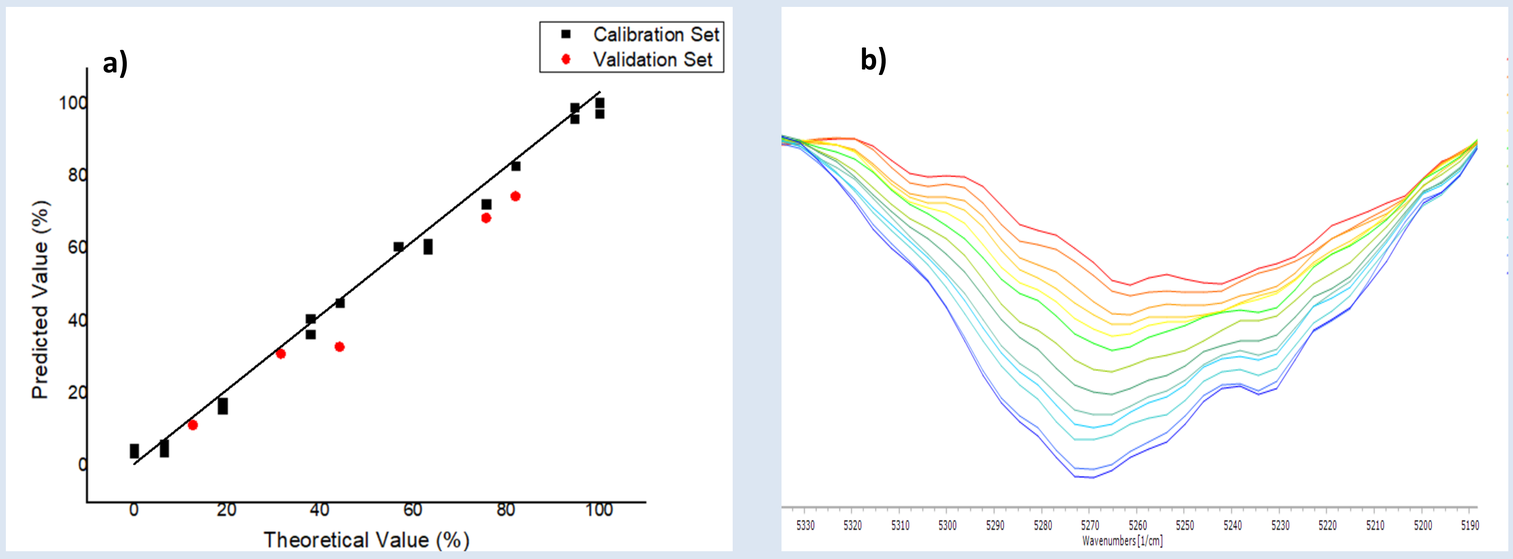

Fig 1. Data obtained from the Near Infrared Spectroscopy analysis
a) Calibration curve and b) Most representative spectral regions

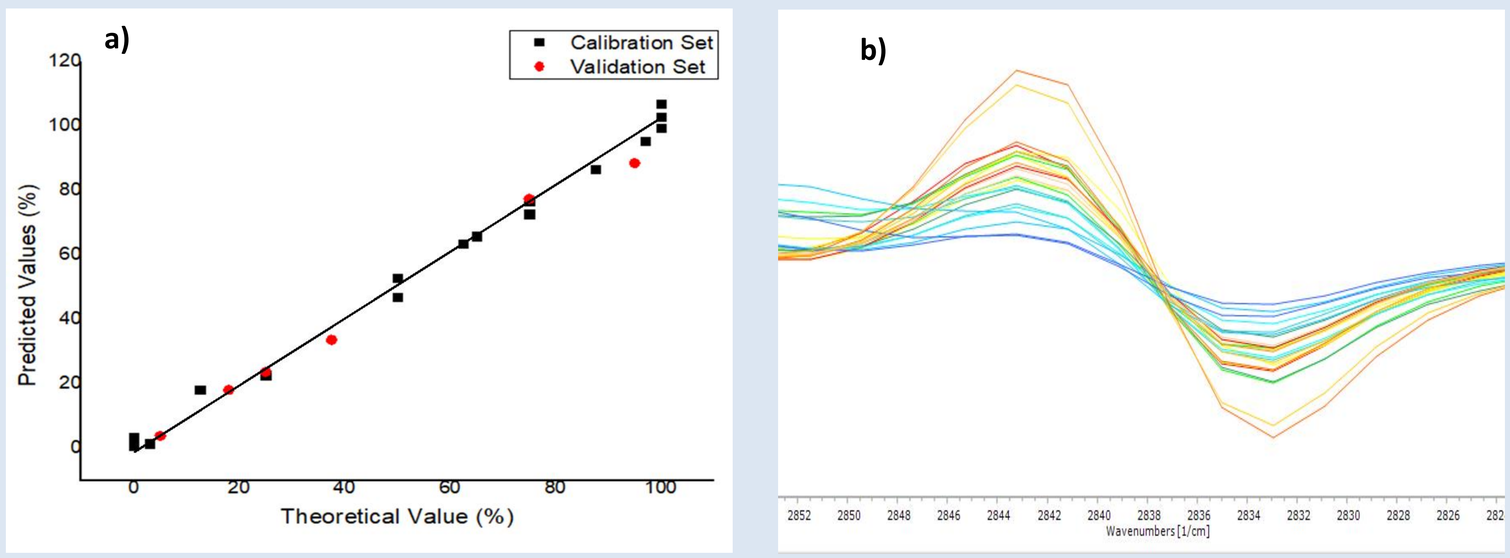

Fig 2. Data obtained from the Fourier-Transform Infrared Spectroscopy analysis
a) Calibration curve and b) Most representative spectral regions

The application of a 1st derivative to both the Near Infrared and Fourier-Transform Infrared spectral data enabled the obtention of models with the lowest error of calibration and validation (Table 1) compared with the other processing methods (e.g. Standard Normal Variate or 2nd derivative).

The high coefficient of correlation found for the model and the low error of validation for the predicted samples, *i.e.*, samples which were not used for the calibration of the model (<5%, for both NIR and FTIR) proved the sensitivity of the methods to evaluate the fraction of amorphous olanzapine within dry and wet masses, as observed in Figures 1 and 2.

Table 1. Error of calibration and validation for both Near Infrared and Fourier-Transform Infrared Spectroscopies using a 1st derivative filter.

Error (%)	NIR	FTIR
Calibration	3.1	2.9
Validation	4.3	2.8

Caption:

Amorphous — Crystalline

Conclusions

Apart of traditional techniques such as Differential Scanning Calorimetry and Powder X-Ray Diffraction, the application of Near Infrared Spectroscopy and Fourier-Transform Infrared Spectroscopy has been shown to constitute valuable methods for expedite quantification of amorphous olanzapine within dry and wet mixtures. Furthermore, these are non-destructive techniques which offer significant advantages such as fast evaluation and use with either dry or wet samples. They are also sensitive enough to be considered in the evaluation of the recrystallization kinetics of drugs, particularly olanzapine, which is expected to happen in mixtures containing either amorphous or co-amorphous olanzapine.

References

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