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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INTRODUCTION

Currently, more than 70% of drugs in R&D show extremely low solubility in water, which ultimately compromise their bioavailability in the human body. 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 the solubility of such drugs. Despite the large increase in solubility presented by the material in the amorphous state, they are highly instable thus preventing or making their use problematic in the pharmaceutical industry due to short and unpredictable stability prior to conversion into a more stable state. 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 (e.g. hydrogen bonds) 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 tendency of the co-amorphous olanzapine (OLZ), a BCS class II drug, and saccharin (SAC).

MATERIALS AND METHODS

A mixture comprising olanzapine and saccharin in a 1:1 molar ratio was dissolved in dichloromethane and then the 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 verify the production of a coamorphous entity.

Different amounts of the OLZ:SAC co-amorphous powder (0-15.8%) were blended with anhydrous dibasic calcium phosphate (46.3%), microcrystalline cellulose (33.7%) and povidone (4.2%) (Table 1). 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 also added to the final mixtures immediately before the analysis of the wet masses.

Exp.	Amorphous OLZ (%, OLZ basis)	H_2O (%, dry basis)
1	0.0	0.0
2	0.0	20.0
3	0.0	40.0
9	25.0	0.0
10	25.0	20.0
11	25.0	40.0
13	50.0	0.0
14	50.0	20.0
15	50.0	40.0
16	62.5	0.0
19	75.0	20.0
26	100.0	20.0
27	100.0	40.0

Table 1. Part of the Design of Experiments (DoE) matrix considered for the development of the monitoring strategy.

Near infrared spectroscopy (NIR) and Fourier transform infrared spectroscopy (FTIR) were considered to evaluate spectral differences between the various formulations containing different fractions of crystalline /amorphous OLZ. Correlations were obtained when Partial Least Square Regression (PLS-R) methodology was applied enabling the development of the model.

RESULTS AND DISCUSSION

After processing all spectra with a second order derivative filter it was possible to obtain a correlation between the spectral regions 4700-4000 cm^{-1} and 6200-5600 cm^{-1} and the quantity of amorphous and crystalline olanzapine present in each sample (Figure 1).

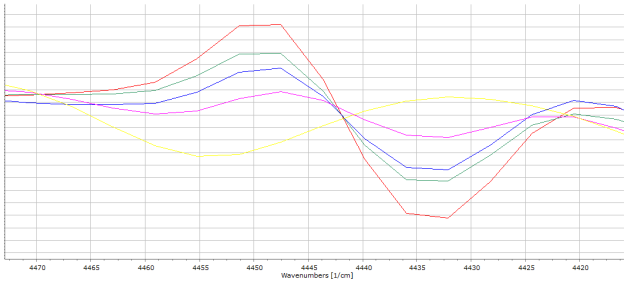

Figure 1. Part of the 2nd derivative spectra (4470-4420cm^{-1}) for 0% amorphous olanzapine (red), 25% amorphous olanzapine (green), 50% amorphous olanzapine (blue), 75% amorphous olanzapine (pink) and 100% amorphous olanzapine (yellow).

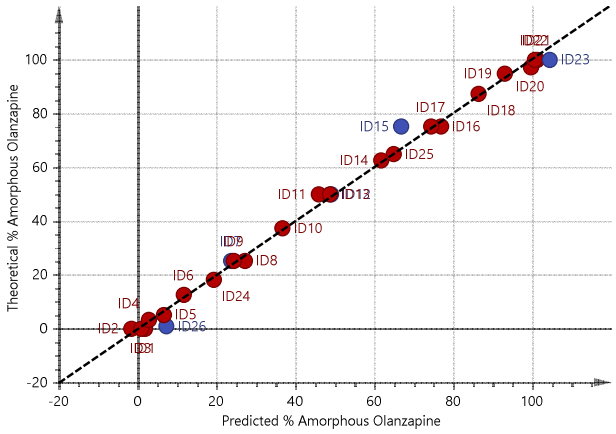

Figure 2. Differences obtained between the expected and the predicted amorphous contents when the model was used.

The high coefficient of correlation found for the model (R^2=0,998) and the low error of validation for the predicted samples, *i.e.*, samples which were not used for the calibration of the model (<5%, Figure 2) proved the sensitivity of the method to evaluate the fraction of crystalline OLZ, predicting both the amorphous and the crystalline fractions of olanzapine in the different mixtures.

CONCLUSION

The work has provided a model to allow a quick, non-destructive and effective method to monitor the recrystallization of amorphous OLZ present in formulations as co-amorphous entities.

The application of spectroscopic analysis (NIR and FTIR) enabled the quantification of crystalline /amorphous OLZ in dry and wet mixtures.

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