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Addressing drug solubility problems. A case-study

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A significant (>70%) number of drugs entering the market present low solubility in water[1]. To minimize this problem, which impacts on dissolution, absorption, and therapeutic efficacy of drugs in dosage forms, several techniques have been employed, namely micronization or the selection of a defined polymorph[2].

The production of amorphous solid dispersions of drugs is regarded as one of the most powerful approaches for solubility enhancement. However, since amorphous substances are thermodynamically unstable, they tend to convert back into a stable crystalline lattice. This conversion can be delayed by the combination of substances producing co-amorphous mixtures[2,3], due to bond formation between individual molecules, thus preventing crystal formation[2].

The aim of this study was to produce a stable co-amorphous entity containing olanzapine, a poorly water soluble antipsychotic drug, with enhanced solubility in water.

Keywords:

Co-amorphous, solubility, molecular interactions, DSC, XRPD, FTIR

References:

[1] Thayer A.M., Finding solutions, Chem Eng News. 2010; 88: 13-8.

[2] Dengale S.J., Grohganz H., Rades T., Löbmann K., Recent advances in co-amorphous drug formulations, Adv Drug Deliv Rev. 2016; 100: 116-25.

[3] Lobmann K., Grohganz H., Laitinen R., Strachan C., Rades T. Amino acids as co-amorphous stabilizers for poorly water soluble drugs - Part 1: Preparation, stability and dissolution enhancement. Eur J Pharm Biopharm. 2013; 85: 873-81.

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MATERIALS AND METHODS

A 1.0g mixture composed of olanzapine and saccharin was dissolved in dichloromethane in a 1:1 molar ratio and the solvent was then removed by evaporation at 40°C.

The resulting mixture was characterized by Fourier-transform infrared spectroscopy (FTIR) and near infrared spectroscopy (NIR) to detect possible interactions between the molecules of each compound present in the mixture and the combination of differential scanning calorimetry (DSC) with X-ray powder diffraction (XRPD) to assess the formation of the amorphous state of the mixture. Solubility studies were also performed in order to evaluate the increase in water solubility of the drug within the co-amorphous entity.

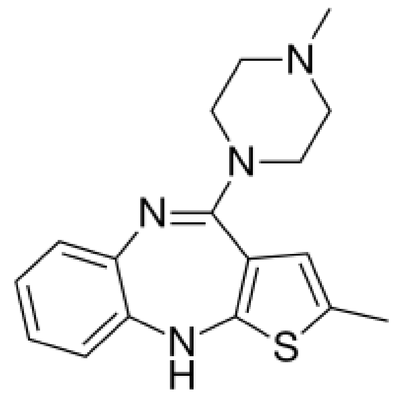

Figure 1. Chemical structure of olanzapine.

RESULTS

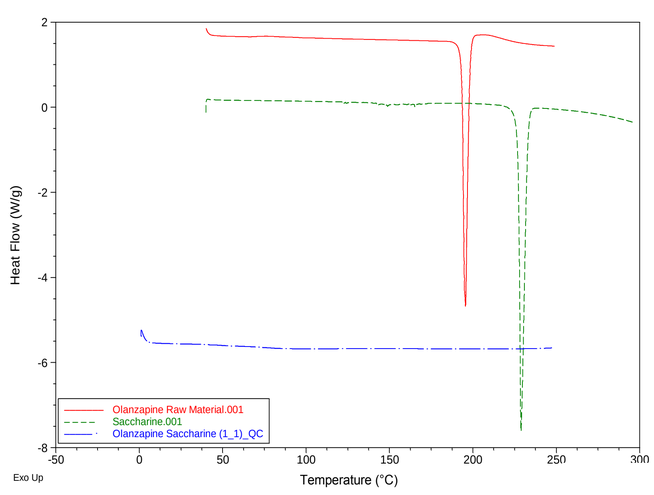

Figure 2. Differential scanning calorimetry thermogram of the co-amorphous olanzapine and saccharin mixture

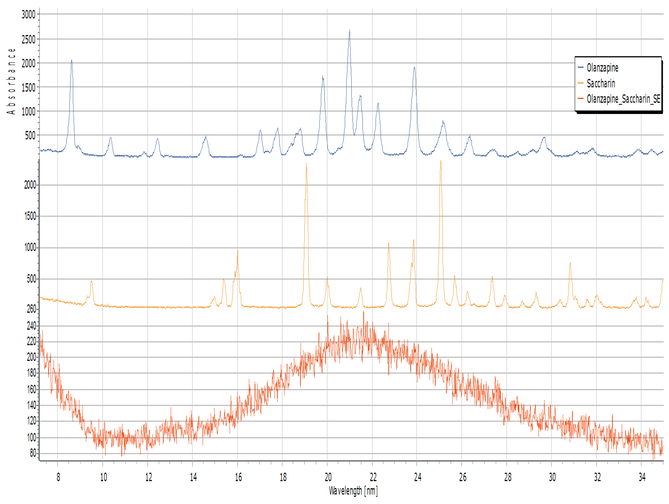

Figure 3. X-ray powder diffraction of the co-amorphous olanzapine and saccharin mixture.

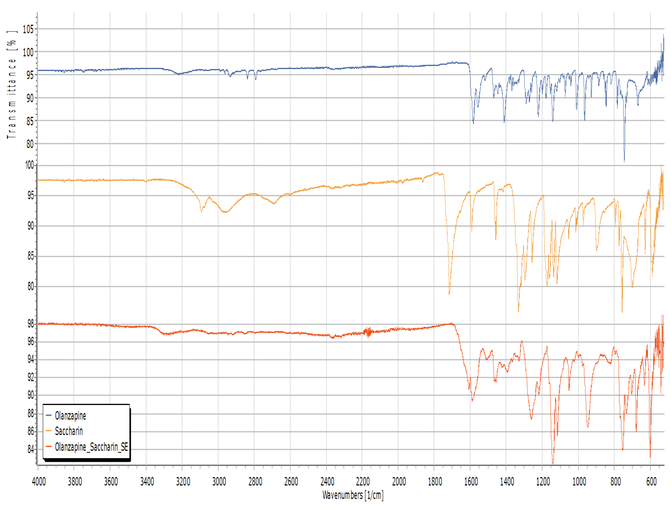

Figure 4. FTIR spectra of the co-amorphous olanzapine and saccharin mixture.

Table 1. Increased solubility of the co-amorphous olanzapine and saccharin mixture

Solubility (g/L))	
Crystalline Raw Material	**Co-amorphous mixture Olanzapine/Saccharin**
0.039	4.45

DISCUSSION AND CONCLUSIONS

Co-amorphous mixtures offer a powerful pathway to promote the water solubility of drugs. This approach is therefore particularly useful for Biopharmaceutical Classification System (BCS) class II and IV drugs. Olanzapine is an antipsychotic BCS class II drug which shows a maximum solubility in water of only 39.0mg/L.

The mixture olanzapine and saccharin produced by dichloromethane evaporation, characterized by combination of DSC and XRPD, has proven to be a co-amorphous entity. The stability of the amorphous complex is justified by the establishment of intermolecular bonds between the compounds present in the system.

The co-amorphous mixture showed an increase in the water solubility of olanzapine of 114 times, as compared to the raw material.