Co-amorphization of olanzapine for solubility enhancement

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Introduction: Nowadays a significant (app. 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 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 combination of substances producing co-amorphous mixtures (2,3), due to bond formation between individual molecules, thus preventing crystal formation (2). The aim of the present study was to assess the potential of several excipients for the production of stable co-amorphous containing olanzapine, a poorly water soluble antipsychotic drug.
Materials and Methods: Mixtures of olanzapine with L-arginine, L-tryptophan, L-proline, citric acid, oxalic acid, tartaric acid, saccharin and caffeine were produced in a 1:1 molar ratio by the quench cooling of molten mixtures with liquid nitrogen. The mixtures were characterized by near infrared spectroscopy (NIR, ABB TLA 20), before and after quench cooling, to detect interactions between the molecules of each compound and differential scanning calorimetry (DSC, TA Instruments QA200, 0-250ºC, at 10ºC/min) to assess the formation of different polymorphic forms of olanzapine. Solubility studies were performed to evaluate the increase in water solubility of the drug.
Results: Thermal analysis revealed that mixtures of olanzapine and L-proline, citric acid, tartaric acid and saccharin were the most promising for the production of co-amorphous mixtures. NIR spectra of these mixtures show an increase in the intensity of absorbance in OH regions (5200-5100cm^{-1}) and the appearance of a band related to NH-OH interaction, likely due to bond formation. The thermograms derived from calorimetric studies did not show any endotherms related to melting of materials. Furthermore, the systems resulted in increased drug solubility, ranging between 28 for L-proline and 57 times when saccharin was used.
Discussion and Conclusions: The screening of the excipients for the potential production of co-amorphous mixtures containing olanzapine allowed the selection of L-proline, citric acid, tartaric acid and saccharin. The binary mixtures were characterized by strong absorbance intensities at the wavenumber corresponding to OH and NH bonds, indicative of the establishment of hydrogen bonds between these groups within the drug:excipient molecules.
In conclusion, the increased solubility, the absence of endotherms related to melting and hydrogen bond formation, strongly suggests co-amorphization of olanzapine with the excipients tested.

References:
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