Addressing drug solubility problems. A case-study

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Abstract:
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 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 this study was to assess the potential of several excipients for the production of stable co-amorphous entities containing olanzapine, a poorly water soluble antipsychotic drug.
Mixtures of olanzapine with amino acids, carboxylic acids and saccharin were produced in a 1:1 molar ratio by quench cooling. The mixtures were characterized by NIR to detect interactions between the molecules of each compound and the combination of DSC with XRPD to assess the formation of different polymorphic forms of olanzapine. Solubility studies were performed to evaluate the increase in water solubility of the drug.
Thermal analysis and XRPD 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 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.

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.