Drug-Excipient and Drug-Drug mixtures: a pathway for the production of co-amorphous entities

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Introduction: Bioavailability is a milestone in drug development, since it reflects the amount of drug absorbed that reaches the site of action. About 70-90% of all drugs in R&D have problems regarding solubility in water, thus presenting low bioavailability (1). Consequently, high doses of drug should be present in the final dosage form to assure therapeutic effect (1), resulting in higher costs for both industry and patients. Co-amorphization is a common strategy to increase the solubility of drugs in water. The co-amorphous systems can be produced with a mixture of active pharmaceutical ingredients (APIs) or a mixture of a drug with one or more small molecular weight excipients (1,2). The purpose of this work was the production of co-amorphous entities with carbamazepine, a class II BCS drug, nearly insoluble in water (3), and the evaluation of which substances (either APIs or excipients) allowed the production of the most stable systems.

Materials and Methods: Mixtures of carbamazepine with indomethacin, olanzapine, L-arginine, L-tryptophan, L-proline, citric acid, oxalic acid, tartaric acid, saccharin and caffeine were produced in a 1:1 molar ratio. The molten pairs of substances were quenched cooled with liquid nitrogen to produce the co-amorphous, which were characterized by near infrared spectroscopy (NIR, ABB TLA 20) to identify possible interactions between the compounds and differential scanning calorimetry (DSC, TA Instruments QA200) to assess the formation of amorphous or other polymorphic forms of carbamazepine.

Results: From the DSC analysis it was possible to identify that drug-drug mixtures (carbamazepine-olanzapine and carbamazepine-indomethacin) were successfully converted into co-amorphous systems. On the other hand, it was not possible to produce co-amorphous of carbamazepine with any of the excipients tested. For the carbamazepine-olanzapine and carbamazepine-indomethacin systems, the NIR spectra shows the disappearance of the peak corresponding to the $CONH_2$ functional group of carbamazepine (5100-6800cm^{-1}). Furthermore, for the system carbamazepine-indomethacin a decrease in the intensity of the NH and OH regions around 5000-4800cm^{-1}, was also found.

Discussion and Conclusions: Carbamazepine was able to produce co-amorphous mixtures with either of the other drugs (olanzapine or indomethacin), while the blends comprising carbamazepine and excipients were not converted to the amorphous state. The formation of the co-amorphous system involved the formation of hydrogen bonds between the functional groups $CONH_2$ and NH or OH, depending on which exist in the molecules. The impact of drug:drug co-amorphization on carbamazepine solubility is under evaluation.

References:

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