Co-crystals of Nevirapine: Preparation methods and solid state characterization.

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Palavras Chave: *Nevirapine, HIV, AIDS, co-crystals*

Introduction

The antiretroviral drug Nevirapine (NVP) (11-Cyclopropyl-5,11-dihydro-4-methyl-6H-dipyrido[3,2-b:2',3'-e][1,4]diazepin-6-one) is a non-nucleoside reverse transcriptase inhibitor, used in the treatment of HIV-1 infection. It is a class II drug according the Biopharmaceutics Classification System (BSC)[1], exhibiting low solubility and high permeability. To increase the drug dissolution and its bioavailability, the different preparation methods with crystal modification such as co-crystals were studied[2]. Co-crystals are multicomponent crystalline solids that can be polymorphs. Co-crystals have different drug molecules or a drug and a non-volatile substance in its structure[3].

NVP molecule has a conformationally rigid amide group that allows a co-crystal formation with soluble carboxylic acids or amide co-formers[2]. Thus, it was developed a synthesis route as alternative to solid forms of the drug, potentially more soluble.

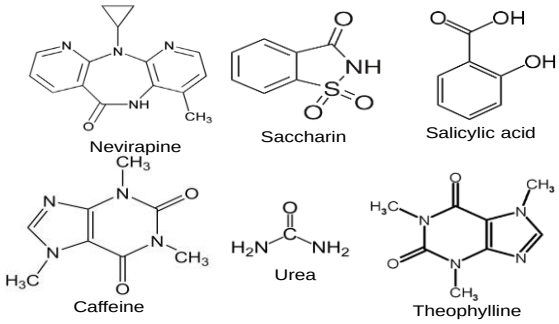
The goal of this work is to develop and evaluate a scalable preparation method to obtain pure forms of co-crystals of NVP. Two methods were evaluated: 1) physical mixture of NVP and co-former with heating; 2) Slurry milling process, with different stoichiometries and solvents: NVP:co-former (1:1 and 2:1), solvents (methanol and chloroform) and different times of grinding (4 and 24 hours). The used co-formers were: Saccharin (SAC), Salicylic acid (AS), Caffeine (CAF), Urea (URE) and Theophylline (TEO). The molecules of Nevirapine and co-formers are showed in figure 1.

The materials were characterized by powder X-ray diffraction (PXRD), scanning electronic microscopy (SEM) and differential scanning calorimetry (DSC).

Results e Discussion

The PXRD data were compared with reported values for 2:1 co-crystal[2]. In NVP:SAC samples were identical to the previously reported co-crystal in both stoichiometries: 1:1 and 2:1, being a pure form. The grinding time and different solvents were not relevant in the co-crystal formation.

Figure 1. Structural formulas of NVP and co-formers.



In NVP:AS samples it was detected the presence of the reported co-crystal[2] for the 2:1 stoichiometry, being a pure form. Meantime, for 1:1 stoichiometry sample it was observed a new crystalline form which could indicate the presence of new co-crystal.

For NVP:CAF, NVP:URE and NVP:TEO it was observed only a mixture of NVP and co-formers in both stoichiometry and not the co-crystal formation.

Promising results and co-crystal formation were detected using physical mixtures of NVP / co-formers with different temperature treatments.

Conclusions

The slurry milling and heating processes are good methods to obtain co-crystals of NVP in high quantity and in pure crystalline forms.

Acknowledgements

CAPES e FIOCRUZ.

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