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Stereochemistry 2016: FTIR, Dissolution and Anti-viral Activity of Nevirapine Co-crystals - Samsodien H - University of the Western Cape

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Introduction

Nevirapine (NV) is a non-nucleoside reverse transcriptase inhibitor used in combination with other antiretroviral drugs for the treatment of Human Immunodeficiency Virus (HIV) infections. NV directly inhibits reverse transcriptase activity therefore suppressing DNA replication of the HIV virus and is known to prevent HIV transmission from mother to infant. A single dose of NV administered to the mother at the onset of labor and to the baby within 72 hours of delivery nearly halved the rate of HIV transmission. Since NV is given only once to the mother and baby it is relatively cheap and easy to administer.

NV is practically insoluble in water with an aqueous solubility of 0.1 mg / ml-1 (pH 7, temperature 37 ° C). According to the biopharmaceutical and classification index, NV is a class II drug, i.e. it has high permeability and low solubility. The slow rate of dissolution of the NV is assumed to be the step limiting the rate of absorption of the drug.

Co-crystals, a crystal structure, containing two or more different components in a defined stoichiometric ratio have been studied to improve the solubility, bioavailability and speed of dissolution of NV. Co-crystals are formed between an active molecular or ionic pharmaceutical ingredient (API) and a co-crystal, where each component is a solid at room temperature and also produces a solid product at room temperature. The co-trainers were selected according to the hydrogen bonding rules to facilitate the non-covalent bond between the molecules. NV co-crystals have been formed with compounds generally considered safe (GRAS), namely saccharin (SC), tac-tartaric acid (TTA), maleic acid (MLE) and salicylic acid (SLI). Glutaric acid (GLT) has also been used as a co-trainer to form NV co-crystals. NVSC and NVSLI formed co-crystals with a 2: 1 ratio of NV to the co-trainer concerned. NVTTA, NVMLE and NVGLT formed co-crystals with a 1: 1 ratio of NV to the co-trainer concerned.

In a similar study, the formulation of nicotinamide-based fenofibrate co-crystals by different methods in a 1: 1 molar ratio was used to formulate molecular complexes by kneading, solution crystallization, addition of anti-solvents and grinding of drops of solvent. . The molecular complexes prepared were characterized by powder X-ray diffractometry, scanning calorimetry, Fourier transform infrared spectroscopy (FTIR), nuclear magnetic resonance spectroscopy and in vitro dissolution analysis. Analytical techniques have all been widely used to distinguish different crystal forms such as polymorphs, clathrates, hydrates and co-crystals. FTIR has also been used to monitor the formation of co-crystals and the detection of a single building block.

Materials and Methods

Hot stage microscopy

The integrity and purity of all co-crystals were checked using microscopy at hot (HSM) before the experiment.

Fourier transform infrared spectroscopy

Fourier transform infrared spectroscopy (FTIR) was performed to confirm the identity of the five co-crystals and to determine if FTIR could be used in future co-crystal studies to identify forms of co-crystals.

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Dissolution testing

The dissolution profile of NV improved for both co-crystals and physical mixtures. NVGLT was the only co-crystal that gave better results than NV and its physical mixture. However, NVGLT and its physical mixture still did not meet the standards of the British Pharmacopoeia 2005 (BP) since 75% of the substances were not dissolved within 45 minutes [6-8]. Only 30% and 26% went into solution after 45 minutes for the NVGLT co-crystal and the NV: GLT mixture, respectively.

Antiviral testing

In vitro antiviral testing of the co-crystals are necessary to confirm that the new crystalline form of NV has comparable or improved activity against HIV-1. The co-crystals showed no significant cytotoxicity to the 293T cells, as percentage viability remained above 50% for all co-crystals tested. The cytotoxicity-50 (CC50) value is greater than the maximum concentration tested, indicating no cytotoxic effect to the 293T cells. These concentration ranges were therefore used when screening for anti-HIV-1 activity.

When testing for antiviral activity, the NICD confirmed that neither the co-formers nor the DMSO solvent inhibited HIV-1. This indicates that the inhibitory activity displayed by the co-crystals is directly the result of the NV portion of the molecule. NVSC and NVSLI had an average IC50 of 0.037 mM, which differed significantly from pure NV (0.083 mM), with p values of 0.002. NVMLE and NVGLT had mean IC50 values of 0.055 mM and 0.054 mM significantly different from pure NV with p values of 0.026 and 0.019, respectively.

Conclusion

The results presented here indicate that FTIR is an appropriate analytical method to identify co-crystals with the exception of co-crystals with a molecular ratio of 2: 1. Since the co-trainer and the NV are held together by de weak hydrogen bonds, peaks were to occur at C = O, OH and NH bonds. The Spectrum software used in this study could only detect the C = O bonds. The dissolution of NV was improved in the presence of individual co-formers, both in the form of a co-crystal and in the form of a physical mixture. NVGLT was the only co-crystal that gave better results than its physical mixture. Solubility studies indicate that the choice of co-trainers for future research could possibly be based on pKa and melting point values. HPLC has proven to be a more precise and precise method of analysis than UV spectrometry, producing more reliable results. Finally, the antiviral activity NVSC, NVSLI, NVMLE and NVGLT HIV-1 differed significantly from pure NV compared to NVTTA.

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