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ABSTRACTS POSTER PRESENTATIONS

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LC-QToFMS studies for the separation, identification, and characterization of degradation products of darunavir

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Darunavir, (3 [(4-amino-benzenesulfonyl)-isobutyl-amino]-1-benzyl-2-hydroxypropyl)-carbamic acid hexahydrofuro-[2,3-b]furan-3 yl ester, is a synthetic non-peptidic protease inhibitor developed in 1998 by the pharmaceutical company Tibotec. The compound was licensed in June 2006 in the United States and in February 2007 in the European Union. It has shown to be extremely potent against wild-type HIV as well as against a large panel of protease inhibitor-resistant clinical isolates and has shown a high genetic barrier to the development of antiretroviral resistance. There is no published analytical method or stability indicative method to evaluate darunavir raw material and tablets, and there is no published stability study of darunavir. Chemical and physical degradation of drugs may result in altered therapeutic efficacy and even in toxic effects. Understanding the factors that change the stability of pharmaceuticals and identifying ways to guarantee their stability are important tasks. Therefore the aim of this study was to develop and validate a RP-LC method to determine darunavir raw material and tablets and in the presence of degradations products. A comprehensive mass fragmentation of darunavir, which has not been reported so far, was established by subjecting the drug to liquid chromatography mass spectrometric (LC-MS) analysis and multi-stage mass spectrometric studies. The objective of the present investigation was to separate, identify, and characterize all the degradation products (DPs) of darunavir, generated under various stress conditions. The drug was subjected to hydrolysis (acid and basic), oxidation, and thermal stress, according with the International Conference on Harmonization (ICH) guideline Q1A(R2). The drug was found to be unstable under acidic, basic, oxidative and thermal stress conditions while it was stable in neutral stress conditions. The degradation products were separated on a C-18 column employing an isocratic high-performance liquid chromatographic (HPLC) method. A complete mass fragmentation pathway of the drug was first established with the help of a QToFMS and 10 MS accurate masses were obtained. Then, stressed samples were subjected to LC–QToFMS studies, which provided their fragmentation pattern and accurate masses. The mass spectral data were employed to characterize the major DPs and assign formulas and tentative structures to them. The total information was also used to establish a tentative degradation pathway of the drug.

Photodegradation Products of Linezolid in Tablets

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Linezolid (LNZ) is a member of a new class of antibiotics, the oxazolidinones. Linezolid (S)-N-[[3-[3-fluoro-4-(4-morpholinyl) phenyl]-2 oxo 5- oxazolidinyl] methyl] acetamide (Fig 1) was the first oxazolidinone to be developed and approved for clinical use. Linezolid is currently the only antimicrobial agent which can be administered orally being rapidly absorbed following oral administration and it is eliminated via renal and non-renal routes. Linezolid has a wide spectrum of activity against gram-positive organisms and appears to be an effective treatment option when compared to vancomycin. The aim of this study was to identify the photodegradation products of linezolid. Linezolid reference substance was obtained from "Synfine research" The linezolid tablets, which were claimed to contain 600 mg of active drug, were obtained commercially. To evaluate the degradation products formed, was used a method previously validated, mobile phase 1% acetic acid: methanol: acetonitrile (50 : 25: 25, v/v/v) and semi-preparative column Zorbax Rx-C18 - 250 mm x 9.4 mm, 5 µm – AGILENT. The samples were collected in HPLC and then inserted by direct infusion MS / MS. All experiments were conducted using a Quattro LC triple quadrupole mass spectrometer instrument (Micromass, Manchester, UK) ions were generated using an electrospray ionization interface (ESI) and detected in the positive ion mode. In the analysis it was possible to detect the formation of photodegradation products in different samples, comparing with the analyzed standard (Figure 1).

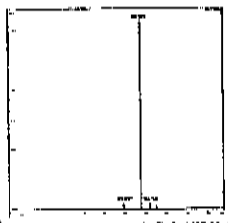

Figure 1. Tandem mass spectr... -2).

In this work it was possible to identify the photodegradation products formed and elucidate the chemical structures of the products.

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