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Mass Spectra 2018: Elucidation of unknown pharmaceutical degradation products: Structures and pathways- Kung Tien Liu- Everlight Chemical Industrial Corporation

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Algorithm for the elucidation of several unknown degradation products shown in the stability studies of Active Pharmaceutical Ingredients (APIs) and drug products, including structures and degradation pathways has been proposed. Collision Activated Dissociation (CID) fragments of APIs and their related intermediates, received using high-performance Liquid Chromatography-tandem Mass Spectrometry (LC-MS/MS) were achieved firstly. Accordingly, Multiple Reaction Monitoring (MRM) ion pairs and fragmentation pathways can be developed secondly. Meanwhile, considering the feasibility of secondary degradation products, core chemical structures that might occur in common in the degradation products were deduced. MRM ion pairs together with related biotransformation scanning (i.e. oxidation (+O, +2O), dehydration (-H2O, -(H2O)2), carbon dioxide removal and HOAc removal) and Information-Dependent Acquisition (IDA) in the target HPLC retention regions were evaluated and compared thoroughly. Finally, unknown degradation products needed to be verified by the stability test samples. Countermeasures, such as pattern of stable isotopic peaks, kinetics studies and interference factors existed in reagents, manufacturing process raw materials and environment such as plasticizer and catalysts were investigated. Unexpected products and interaction between excipients were also identified. Today, it is necessary to identify relevant compounds appearing in discovery and development of new drug substances in the pharmaceutical industry. For that purpose, the measurement of accurate molecular mass and empirical formula calculation is very important for structure elucidation in addition to other available analytical methods. In this work, the identification and confirmation of degradation products in a finished dosage form of the antibiotic drug amoxicillin obtained under stress conditions will be demonstrated. Structure elucidation is performed utilizing liquid chromatography (LC) ion trap MS/MS and MS^3 together with accurate mass measurement of the molecular ions and of the collision induced dissociation (CID) fragments by liquid chromatography electro spray ionization time-of-flight mass spectrometry (LC/ESI-TOF). In modern pharmaceutical drug discovery and development, it is of crucial importance to identify unknown compounds with the highest possible confidence because of their potential pharmacologic effects on humans. Such compounds could be, for instance, the pharmaceutically active substances themselves, minor byproducts emerging during the production process, secondary substances in drugs isolated from a natural source, metabolites created in the human body, or degradation products of the pharmaceutical agent arising during storage. In addition to the repertoire of analytical methods for structure elucidation, the mass spectrometric measurement of accurate molecular mass and, consequently, the determination of the empirical formula is a common strategy for the identification of unknown compounds. Until a few years ago, the only instruments available to perform these measurements with highest mass accuracy were the magnetic sector mass spectrometers. Nowadays, ESI orthogonal acceleration TOF (oaTOF) instruments are also capable of handling this task sufficiently for compound confirmation. This is demonstrated by a comparison study of different types of mass spectrometer instruments for the determination of accurate masses of small molecules. The improved molecular mass determination capability of oaTOF instruments was made possible by several technical innovations in TOF technology introduced during the past few years. One of the main technical improvements is the development of orthogonal acceleration (oa) TOF technology, which decouples ion beam velocity spread from the TOF axis and therefore provides better resolution. In such an environment, today's routine of coupling continuous ionization sources like the electrospray ionization (ESI) source with oaTOF mass analyzers is of special importance for LC/ESI-TOF applications. High mass accuracy is only achieved when a reference compound, e.g., a reference mass solution, is simultaneously introduced into the mass spectrometer. However, mixing the LC column effluent with a stream of reference material can result in ion suppression, discrimination, or adduct formation. To preclude the need for mixing the analyte and the reference compound before spray ionization, a dual sprayer interface is used for ESI . Such an instrument is capable of achieving resolving powers of better than 15,000 and mass accuracies in the low single digit ppm range for small molecules . Recently, the implementation of oaTOF instruments for the measurement of accurate molecular mass, the calculation of the empirical formula, and consequently, the identity confirmation of an unknown compound, was impressively demonstrated for a large number of published applications. For instance, LC/ESI oaTOF was used for the characterization of in vitro drug metabolites by accurate mass measurement of the molecular ion and the CID fragments The instrument found its place for the quantification and accurate mass measurement of pharmaceutical drugs in plasma as well as for the characterization of trace level impurities in a drug substance . In conjunction with an ion trap instrument for MS/MS and MS^3 experiments to gain structural information, the ESI oaTOF was used for the identification of a photooxygenation product of a broad spectrum antibiotic used for live stock and for the identification of highly complex polyene macrolides isolated from *Streptomyces noursei* by means of an ion trap monitored purification process.

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Biography

Kung Tien Liu has completed his PhD from Department of Chemistry, National Taiwan University, Taiwan and has worked in Institute of Nuclear Energy Research (INER) more than 29 years. He also concentrates his major activities on the GxP related compliance issues for the development and applications of pharmaceuticals. Currently, he is the Deputy Director of Administration Office, Pharmaceutical B U, Everlight Chemical Industrial Co. (ECIC). He has been published more than 40 papers, patents and book chapters.

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