

Rapid Analysis of Pharmaceuticals and their Metabolites with Atmospheric Pressure Infrared MALDI Mass Spectrometry

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Novel Aspect: AP IR-MALDI was demonstrated for high throughput analysis of drugs and their metabolites and for pharmacokinetics investigations under ambient conditions.

Introduction

Matrix-assisted laser desorption/ionization (MALDI) mass spectrometry (MS) is a well established tool for the analysis of biomolecules and synthetic polymers. Due to interferences from the matrix molecules, the analysis of small molecules, such as pharmaceuticals and their metabolites, with conventional ultraviolet (UV) MALDI MS has been limited. The application of matrix also requires wet chemistry and thus precludes the possibility of rapid direct analysis. Using the native water content in biological samples as the matrix results in dramatically reduced mass spectral interference. We explored the utility of atmospheric pressure (AP) infrared (IR) MALDI MS for the direct analysis of pharmaceuticals and their metabolites in biological fluids.

Methods

A Q-TOF Premier time-of-flight (TOF) mass spectrometer (Waters Co., Milford, MA) was retrofitted with a custom made AP MALDI interface. To improve the ion collection efficiency, the ions produced by a Nd:YAG laser-driven optical parametric oscillator (running at 2.94 micrometer and 10 Hz) were sampled into the mass spectrometer using pulsed dynamic focusing. The method had been described in detail in Y. Li, B. Shrestha and A. Vertes, *Anal. Chem.*, 2007, 79, 523. Drugs formulated as tablets or gel caps were directly applied to the stainless steel probe. Urine samples were frozen onto the liquid nitrogen cooled probe and stayed frozen for the time of the experiment.

Preliminary results

AP IR-MALDI MS was successfully applied to the direct detection of small molecules such as formulated drugs, and drug metabolites. Various common over-the-counter medications and standards formulated as gelatin capsule, syrup, tablet or powder were directly analyzed with minimal sample preparation. The examples of drugs analyzed include acetaminophen, caffeine, dextromethorphan, doxylamine, guaifenesin, ibuprofen, ketoprofen, loratadine, melatonin, naphthoquinone, pseudoephedrine, salicylamide and verapamil. The drugs were analyzed in both positive and negative modes and structural information on the ions was obtained from MS/MS experiments. The drug metabolite analysis was performed on urine samples collected a few hours after the ingestion of the medication. Both the active ingredients such as pseudoephedrine, acetaminophen and some inactive ingredients, such as PEGs, of a cold medication were detected in the urine sample. AP IR-MALDI can expedite the small molecule analysis in biological samples by minimizing sample preparation time and eliminating the need to transfer the sample into vacuum. One to three microliters of a pharmaceutical sample could typically be analyzed within one second, whereas biological samples took three to five seconds. Tandem MS/MS analysis was generally completed within a minute. The detection limit for a typical pharmaceutical molecule, such as pseudoephedrine, was found to be in low femtomole range.