DEVICE AND METHOD FOR ANALYSIS OF BIOFLUIDS BY ION GENERATION USING WETTED POROUS MATERIAL

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a U.S. National Stage Application of International Patent Application No. PCT/US2016/017306, filed Feb. 10, 2016, which claims the benefit of U.S. Provisional Patent Application Ser. No. 62/114,287, filed on Feb. 10, 2015 and of U.S. Provisional Patent Application Ser. No. 62/293,231, filed on Feb. 9, 2016, the entire disclosures of which are hereby expressly incorporated by reference.

STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT

This invention was made with government support under 2014-R2-CX-K007, awarded by the National Institutes of Justice. The Government has certain rights in this invention.

FIELD

The present disclosure relates generally to a device for simplified analysis of biofluids by paper-spray mass spectrometry and methods of use thereof.

BACKGROUND

Mass spectrometry (MS) is one analytical chemistry technique that helps to identify the amount and type of chemicals present in a sample by measuring the mass-to-charge ratio and abundance of gas-phase ions. There are several steps required to perform MS analysis on complex samples. In some uses of MS, these steps include extraction, preconcentration, and sample ionization. These steps can cause certain MS tests to be time-consuming, expensive, and complex.

MS is the gold standard for performing trace analysis in complex mixtures, but many laborious sample preparation steps generally must be carried out in the laboratory to perform the analyses.

Ion generation using wetted porous material has simplified certain applications of MS. Exemplary systems and methods for ion generation using wetted porous material, such as, for example, paper-spray ionization, have been disclosed and claimed in U.S. Pat. No. 8,859,958, issued Oct. 14, 2014, the entire disclosure of which is hereby expressly incorporated herein by reference.

Paper-spray MS could have a significant impact as a rapid and simple method to assess patient compliance in methadone clinics, pain management clinics, in psychiatric patients, etc. While immunoassays are widely used for this purpose, their limitations for drug screening are well-known, including inadequate sensitivity and selectivity, which can result in false negatives and unacceptably high false positive rates. Faster and simpler methods for analyzing organic contaminants such as pharmaceuticals, abused drugs, pesticides, and personal care products in environmental samples are needed. River or ground water monitoring is challenging because the detection limits required are low, often in the low part per trillion (ppt) range. Improvements in selectivity and on-cartridge sample preparation methods would be a significant improvement over existing methods.

Driven by the desire to increase sample throughput and to perform MS based assays outside of a traditional analytical laboratory, there is a strong and growing interest in developing MS methods that are faster, simpler, and require less or even no sample preparation prior to analysis. Progress in this field accelerated rapidly with the discovery of two "ambient ionization" or "direct analysis" methods in 2004 and 2005, so-called because samples can be analyzed directly in ambient conditions without sample preparation. The two methods, desorption electrospray ionization (DESI) and direct analysis in real time (DART), helped to spark a new research field within the analytical community that has resulted in an array of new applications and new technologies that dramatically simplify MS based assays.

Paper-spray MS is a method for performing rapid, direct analysis of samples spotted on paper or another porous substrate. A liquid sample (e.g., blood or other biofluids, waste water, etc.) is spotted onto the paper and stored as a dried spot. Analysis is performed by depositing a small volume of solvent to the paper where it wicks through the porous substrate and sample by capillarity. The paper, which in some instances is cut to a sharp point, is positioned a few millimeters away from the atmospheric pressure inlet of a mass spectrometer and a high voltage (3-5 kV) is then applied directly to the paper, inducing an electrospray at the tip of the paper. The solvent evaporates from the charged droplets generated by the electrospray process, leaving gas phase ions of the analyte molecules which can then be detected by a mass spectrometer. Chemicals which are both soluble in the extraction/spray solvent and ionizable will be detected immediately by the mass spectrometer provided they are sufficiently concentrated.

Analytes are detected immediately if they are not appreciably retained by the short distance of substrate they travel through. The entire analysis takes about 60 seconds and requires only the paper substrate on which the sample is already stored, a small amount of solvent, and an electrical connection to a low-current, high voltage power supply.

Paper-spray has a number of advantages for performing rapid chemical analysis of complex samples by MS. Paper-spray requires no sample preparation. Direct analysis of blood, urine, and waste-water, has been demonstrated. Single digit ng/mL or sub-ng/mL detection limits for drugs, pharmaceuticals and other small molecules from these complex matrices are currently routine on commercial triple quadrupole mass spectrometers. The sample volume required for paper-spray is low. Methods published in the literature use between 0.5 μL and 15 μL of sample. The small sample consumption of paper-spray is a significant advantage for volume limited samples.

Moreover, the paper substrate doubles as an ionization source and as a sample storage medium. Storage of dried biofluid samples in particular is known to improve sample stability at room temperature. The paper substrate is inexpensive and readily available. Clogging, which commonly occurs in conventional capillary electrospray ionization, is unlikely in paper-spray due to the multi-porous nature of the substrate. Carryover is not a problem because the ion source and everything that contacts the sample is discarded after each analysis. The amount of solvent required per sample is low (less than 100 μL), and all of the solvent is consumed so there is no solvent waste to dispose.

Also, the need for liquid chromatography is removed, which simplifies the analysis and removes common sources of failure in HPLC-MS assays, such as leaks and clogged columns.