

## MULTIPLE SAMPLE INTRODUCTION MASS SPECTROMETRY

### RELATED APPLICATIONS

[0001] The present application claims all rights of priority to U.S. Provisional Application Ser. No. 60/058,683, filed Sep. 12, 1997, U.S. Provisional Application Ser. No. 60/076,118, filed Feb. 27, 1998, and U.S. Provisional Application Ser. No. 60/087,256, filed May 29, 1998, the disclosures of which are fully incorporated herein by reference.

### BACKGROUND OF THE INVENTION

[0002] Atmospheric Pressure Ionization (API) Sources including Electrospray (ES), Atmospheric Pressure Chemical Ionization (APCI) and Inductively Coupled Plasma (ICP) ion sources interfaced to mass analyzers are typically operated with a single sample introduction probe. In mass spectrometric applications where internal standards are required, additional components can be added to the primary sample solution where the resulting mixture is delivered through one probe into the API source. The mixture of compounds in a single solution introduced through the same probe are ionized and mass analyzed. A known sample when mixed with an unknown sample can serve as an internal mass scale or quantitation calibration standard for the unknown components peaks appearing in the mass spectrum acquired in this manner. However, mixing a known compound calibration solution with an unknown sample solution can have undesired analytical consequences. The known and unknown solution components may effect one another in an unpredictable manner during the solution transport or ionization process. One component may react with another in solution or one or more components may suppress the ionization efficiency of other components during the ionization process. A solution with a known component mixture may be difficult to eliminate as a source of chemical contamination in a probe which is running a series of unknown samples at the trace component level. If it is desirable to deliver a known solution as a mixture through the sample introduction probe on an intermittent basis, the occasional sample introduction will be subject to the constraints of solution flow rates through the probe, efficiency of mixing solutions, dead volume losses and flushing of the probe to eliminate the known solution prior to the next analysis. The invention avoids performance and sample introduction problems encountered when mixing liquid samples prior to ionization in an API source, by conducting simultaneous mass analysis of two different solutions without the need to mix solutions in the same probe prior to analysis. One aspect of the invention is the configuration and simultaneous operation of multiple probes or multiple sprayers or nebulizers within a probe assembly through which different sample solutions can be introduced simultaneously into an API source during operation.

[0003] In one embodiment of the invention, multiple sample introduction means have been configured in Electrospray Atmospheric Pressure Ion sources which are interfaced to mass analyzers. At least two sample introduction Electrospray probes are operated simultaneously in an Electrospray ion source. At least one ES probe is supplied a sample which is different from the sample solution supplied to additional ES probes operating within the same ES source chamber. In this manner a calibration solution can be intro-

duced through one ES probe while an unknown sample is introduced through another ES probe or second channel within the same ES probe assembly. Ions produced from both solutions via the simultaneous spraying of both ES probes blend or mix in the atmospheric pressure ES chamber background gas prior to entering the orifice into vacuum. The mixture of ions resulting from the solutions delivered from at least two ES probes is simultaneously mass to charge (m/z) analyzed resulting in a mass spectrum containing an internal standard for calibrating or tuning the mass analyzer. The internal calibration standard contained within the acquired mass spectrum is achieved without mixing known and unknown samples in solution. Simultaneous introduction of different samples through multiple ES probes also enables the study of mixed ion and molecule reactions at atmospheric pressure in the ES source chamber prior to introduction into vacuum. Each ES sample introduction probe assembly can be configured with nebulization gas and liquid layered flow. An internal calibration solution can be included in the layered flow or the primary flow of any given ES probe configured in the ES source chamber. The individual sample solution flows or nebulization gas flows to any combination of ES probes can be switched on or off during an analytical run without the need to reposition probes. In another aspect of the invention, an Atmospheric Pressure Chemical Ionization (APCI) source assembly can be configured with multiple inlet channels or probes. These multiple APCI inlet probes can include pneumatic nebulization and the solution and gas flow supplied to each inlet probe can be individually or simultaneously turned on or off. In both the ES and APCI sources, multiple probe sample solution ionization can be controlled without the need to reposition probes by switching voltages, controlling the nebulization gas flows or controlling the sample solution flows. Configurations of multiple sample introduction inlet probes can also be extended to a system that has a combination of both Electrospray and APCI ion production means in the same API chamber. Each ES or APCI sample inlet probe can include pneumatic or ultrasonic nebulization.

[0004] Configurations of Electrospray ion sources which include more than one sample introduction needle or nebulizer have been described in the literature. Kostianinen and Bruins, Proceedings of the 41st ASMS Conference on Mass Spectrometry, 744a, 1993, described the configuration and use of an assembly of multiple Electrospray inlet tips with and without pneumatic nebulization mounted in an Electrospray ion source. Each ES tip was supplied the same sample solution delivered from a single pump with a single solution source. The sample solution, delivered from a liquid chromatography pump, flowed into an assembly or array of one, two or four ES or pneumatic nebulization assisted ES sprayer tips in an attempt to improve ion signal intensity at higher liquid flow rates. In the arrangement reported, the solution flow to individual sprayer tips could not be turned on and off independently and different solutions could not be introduced selectively to individual sprayer tips in the assembly of multiple ES sprayer tips.

[0005] Rachel R. Ogorzalek Loo, Harold R. Udseth, and Richard D. Smith, Proceedings of the 39th ASMS Conference on Mass Spectrometry and Allied Topics, 266-267, 1991 and J. Phys. Chem., 6412-6415, 1991 and Richard D. Smith, Joseph A. Loo, Rachel R. Ogorzalek Loo, Mark Busman, and Harold R. Udseth, Mass Spectrometry Reviews, 10, 359-451, 1991 describe the configuration of an