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Enhancement of ionization efficiency of mass spectrometric analysis from non-electrospray ionization friendly solvents with conventional and novel ionization techniques

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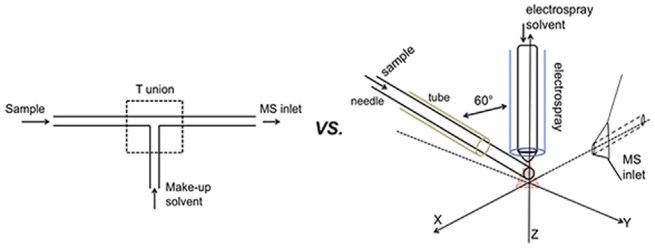
HIGHLIGHTS

- Analyte in non-ESI friendly solvents are ionized with make-up solvent addition or CF-EDESI.
- Sample flow rate and solvent flow rate are important factors affecting ionization efficiency.
- Enhanced and reproducible ionization achieved for non-ESI friendly solvents with either the make-up solvent addition or CF-EDESI.
- Make-up solvent addition provides higher ionization, solvent compatibility and simplicity.
- Matrix effect is not reduced with either make-up solvent addition or CF-EDESI.

GRAPHICAL ABSTRACT



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ABSTRACT

Electrospray ionization mass spectrometry (ESI-MS) has significantly impacted the analysis of complex biological and petroleum samples. However ESI-MS has limited ionization efficiency for samples in low dielectric and low polarity solvents. Addition of a make-up solvent through a T union or electrospray solvent through continuous flow extractive desorption electrospray ionization (CF-EDESI) enable ionization of analytes in non-ESI friendly solvents. A conventional make-up solvent addition setup was used and a CF-EDESI source was built for ionization of nitrogen-containing standards in hexane or hexane/isopropanol. Factors affecting the performance of both sources have been investigated and optimized. Both the make-up solvent addition and CF-EDESI improve the ionization efficiency for heteroatom compounds in non-ESI friendly solvents. Make-up solvent addition provides higher ionization efficiency than CF-EDESI. Neither the make-up solvent addition nor the CF-EDESI eliminates ionization suppression of nitrogen-containing compounds caused by compounds of the same chemical class.

1. Introduction

Since its introduction in 1984, electrospray ionization (ESI) combined with mass spectrometry (MS) has been widely used for analysis of biomolecules [1–6], pharmaceuticals [7], and elemental

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speciation [8,9]. In direct ESI-MS analysis, the liquid sample is infused into the MS inlet through a capillary. A high voltage (3–5 kV) is applied between the capillary tip and the MS inlet to produce charged droplets at the tip of the capillary. The build-up of the charged droplets at the liquid surface causes the formation of a Taylor cone. When the electrostatic repulsion between ions in the Taylor cone overcomes the surface tension of the liquid, the Taylor cone turns into a liquid filament. When the filament becomes unstable, isolated charged droplets are formed. The charged droplets go through solvent evaporation and repeated disintegration to form gas-phase ions. The singly or multiply charged gas-phase ions are separated and detected by a MS analyzer [10]. With the development of various high resolution MS analyzers, the application of ESI-MS has been expanded to complex samples such as in proteomics [1,11,12] and petroleomics [13–15].

ESI-MS experiences some limitations when applied to such complex samples. High resolution ESI-MS can differentiate thousands of chemicals in a mixture [13,14], but it cannot distinguish between isomers of the same mass to charge ratio. In addition, when using ESI-MS to analyze complex samples, matrix components may suppress analyte ionization [16,17]. Ion suppression makes the identification and quantification of chemicals of interest difficult, especially when the matrix compounds are present in significant excess [18]. To compensate, a pre-separation is helpful for the analysis of complex samples.

Combining high performance liquid chromatography (HPLC) with ESI-MS has been widely used for biomolecules [19–23], pharmaceuticals [19,20,24] and environmental samples [25–27]. The hyphenated technique can analyze compounds ranging in size from small molecules to large biological macromolecules. However, the sensitivity and selectivity is highly dependent on the separation technique. Reverse phase liquid chromatography (RPLC) is most frequently used prior to ESI-MS analysis, because of the high polarity and low surface tension of the common organic solvents (e.g. methanol and acetonitrile) used. Ion exchange (IEX) [28,29], ion pair [30–32] and size exclusion chromatography [33] have also combined with ESI-MS. These separation techniques are most suitable for samples that are polar and can be separated with polar mobile phases such as methanol and acetonitrile.

For hydrophobic and isomeric compounds, normal phase liquid chromatography (NPLC) conditions and solvents are most suitable. NPLC uses mobile phase solvents with low polarity, low conductivity and low dielectric constant (e.g., hexane or heptane with a small percentage of isopropanol). Such NPLC solvents are not compatible with the electrospray ion generation, and so NPLC cannot be readily coupled with ESI-MS. Two approaches have been developed to combine NPLC with ESI-MS. Firstly, an ESI-MS compatible solvent, called the *make-up solvent*, is added to the NPLC eluent after the separation [34–36]. The addition of make-up solvent is achieved by connecting the NPLC column to the MS inlet using a T union [34–36], Y union or coaxial flow [37]. Coupling of NPLC with ESI-MS through addition of a make-up solvent has been used for analysis of chiral drugs [34,35], plant lipids [38], and petroleum [39]. Methanol [40], isopropanol [35,36] and ethanol/water [41] with acidic or basic additives are common make-up solvents. Reported flow rates of the make-up solvent have been both higher [35] and lower [38,40] than the flow rate of the eluent. In many cases, the flow rates of the make-up solvent and eluent are not stated [36,39]. In some cases, make-up solvent is not needed, for instance when the NPLC separation uses a mobile phase containing isopropanol (IPA) [42,43]. However, the literature is not clear when a make-up solvent is needed or how much make-up solvent should be added to the eluent to achieve optimal ionization.

The second approach to coupling NPLC to MS is the ambient ionization. This approach requires little or no sample pretreatment, and enables direct and high throughput analysis of biological [44–46], pharmaceutical [47], environmental [48] and fuel [49] samples. Ambient ionization techniques are also claimed to be more matrix tolerant and provide higher ionization efficiency of samples in non-ESI friendly solvents [50].

The design of an ambient ionization usually consists of: a desorption step; followed by a post-ionization step. The desorption can be done by direct desorption or assisted by nebulization, laser adsorption or thermal evaporation, as reviewed in Ref. [51]. Common post-ionization methods are electrospray ionization and atmospheric pressure chemical ionization (APCI) [50,51].

Many combinations of desorption and post-ionization methods have been developed over the past ten years [51]. Desorption electrospray ionization (DESI) was the first and is the most popular ambient ionization technique [52]. DESI uses charged solvents emitted from an electrospray nebulizer to impinge on the sample surface to achieve direct desorption and ionization at the same time. DESI is most suitable for direct analysis of both solid and liquid samples, particularly for samples on flat surfaces [53,54] or biological tissue imaging [55]. Extractive electrospray ionization (EESI) [56] uses an additional electrospray nebulizer to analyze liquid or aerosol samples. The sample is nebulized by a sprayer, and then a second sprayer generates charged solvent droplets. When the nebulized sample meets the charged solvent droplets, analytes are extracted into the solvent droplets and form analyte ions [51,56]. Continuous flow-extractive desorption electrospray ionization (CF-EDESI) is a comparable technique which was recently reported by Schug and coworkers for samples in non-ESI friendly solvents [46,57,58]. Instead of using a sprayer to nebulize the samples as in EESI, CF-EDESI utilizes a needle to provide a continuous flow of the sample in a non-polar solvent [46,57]. Charged solvent (methanol/water mixture) droplets produced by an electrosprayer assists desorption and extraction of analytes in the continuous flow of sample in a non-polar solvent. CF-EDESI has been applied to chiral separations using hexane mobile phase [58]. The sensitivity of NPLC-CF-EDESI-MS has been compared with NPLC-UV detection for amine-containing chiral compounds analysis [58]. Other ambient ionization such as solvent-assisted electrospray ionization (SAESI), is also reported to coupling NPLC with ESI-MS [59].

There is literature that compares different ambient ionization techniques and their mechanism [50,51,57]. However, no comparison of the performance of the CF-EDESI vs. conventional make-up solvent addition has been reported. Our objective in this paper is to address the gap in knowledge with regard to the performance of the conventional (make-up solvent addition) and the novel (CF-EDESI) technique. We have optimized the ionization of directly infused analyte in a non-ESI compatible solvent with both make-up solvent addition and a CF-EDESI source. The suitability of both techniques for samples in non-ESI compatible solvent is investigated and the ionization efficiencies are compared. We also studied the suitability of both techniques for petroleum type standards analysis with ESI-MS. Matrix effects are also studied.

2. Experimental

2.1. Materials

HPLC grade hexane, isopropanol (IPA) and dichloromethane (DCM) were from Fisher Scientific (Fairlawn, NJ, USA). LC-MS grade methanol (MeOH), toluene, progesterone, pyridine, quinoline (99.8%), acridine (99.8%), phenanthrene, and dibenzothiophene were from Sigma–Aldrich (St. Louis, MO, USA). Acetic acid (glacial, >99.7%, HOAc) was from Caledon (Georgetown, ON, Canada). Deionized water (>18.0 MΩ) was from a Barnstead E-pure system.