



Reduced matrix effects for anionic compounds with paired ion electrospray ionization mass spectrometry



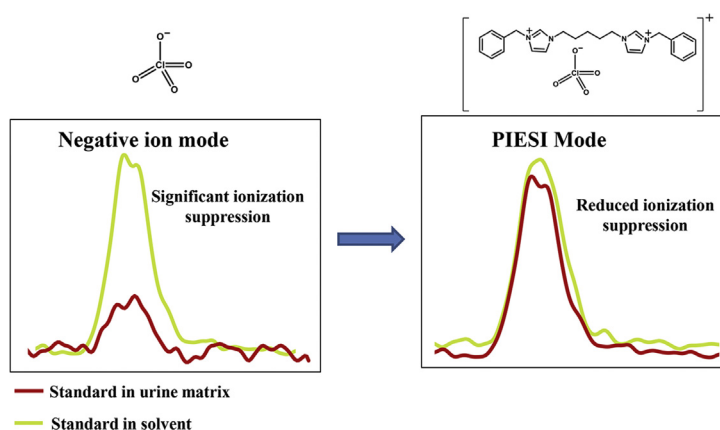
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HIGHLIGHTS

- Reduced matrix effects in groundwater and urine with PIESI-MS of anionic compounds.
- Applicable to both a linear ion trap and a triple quadrupole mass spectrometer for reduction of matrix effects.
- With PIESI-MS, matrix effects were minimized in groundwater or urine matrices.
- In high levels of matrices, samples required less dilution to eliminate matrix effects.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:

Received 13 October 2015

Received in revised form

6 January 2016

Accepted 17 January 2016

Available online 28 January 2016

Keywords:

Paired ion electrospray ionization (PIESI)
Electrospray ionization mass spectrometry (ESI-MS)

Matrix effects

Sensitivity

Linear ion trap

Triple quadrupole

ABSTRACT

It is well-known that matrix effects in high performance liquid chromatography coupled to electrospray ionization mass spectrometry (HPLC-ESI-MS) can seriously compromise quantitative analysis and affect method reproducibility. Paired ion electrospray ionization (PIESI) mass spectrometry is an approach for analyzing ultra-low levels of anions in the positive ion mode. This approach uses a structurally optimized ion pairing reagent to post-column associate with the anionic analyte, subsequently forming positively charged complexes. These newly formed complex ions are often more surface-active as compared to either the native anion or the ion pairing reagent. No studies have examined whether or not the PIESI approach mitigates matrix effects. Consequently, a controlled study was done using five analytes in highly controlled and reproducible synthetic groundwater and urine matrices. In addition, two different mass spectrometers (linear ion trap and triple quadrupole) were used. Compared to the negative ion mode, the PIESI-MS approach was less susceptible to matrix effects when performed on two different MS platforms. Using PIESI-MS, less dilution of the sample is needed to eliminate ionization suppression which, in turn, permits lower limits of detection and quantitation.

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1. Introduction

High performance liquid chromatography coupled with

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electrospray ionization mass spectrometry (ESI-MS) has become one of the most powerful qualitative and quantitative analytical tools. It is characterized by precision, robustness, high sensitivity and selectivity, allowing for the analyses of trace amounts of target compounds in complex mixtures [1,2]. Despite these advantages, one important limitation associated with this technique is its susceptibility to matrix effects [3]. A matrix effect is defined as the effect of extraneous co-eluting components on the ionization efficiency of the target analyte [4,5]. The presence of such matrix components may cause either ionization suppression, or in some cases, ionization enhancement in ESI, leading to quantification errors. Matrix effects also can compromise the limit of detection (LOD), limit of quantification (LOQ), linearity, precision, accuracy and reproducibility of LC-ESI-MS methods [6–8]. Indeed, matrix effects have been called the “Achilles heel” of quantitative HPLC-ESI-MS [9]. Currently, the US Food and Drug Administration's (FDA) guideline documents require the evaluation of matrix effects during the development and validation of HPLC-MS methods, to ensure no loss of the accuracy, selectivity and sensitivity [3,10,11].

The mechanisms of matrix effects have not been fully understood since their initial description by Kebarle and Tang in 1993 [12]. Matrix effects emanate from many sources such as trifluoroacetic acid additives [13], endogenous and exogenous compounds, substances introduced from sample preparation steps [8], and the presence of other co-eluting analytes. Also, factors such as high concentration, polarity, mass and basicity of co-eluting compounds further exacerbate/enhance matrix effects [14].

The origin of matrix effects is thought to be related to the mechanism of ESI. During the ESI droplet formation process, co-eluting matrix components may outcompete target ions for the limited space or charge available at the surface of the droplets, thus, inhibiting ejection of the analyte ions trapped inside the droplets [14–16]. The surface activity is a major characteristic that affects the capability of an ion to reach the surface of a droplet [3,17,18]. Therefore, if a matrix contains undetected components with potentially high surface activities, ionization suppression is common [19]. Another factor that contributes to matrix effects is the solvent evaporation subsequent to droplet formation. The presence of nonvolatile compounds and/or high concentrations of interfering compounds may alter the viscosity and surface tension of the ESI droplet. Consequently, it is more difficult for the solvent to evaporate and this inhibits target ion transfer to the gas phase [5,13,20,21]. Additionally, co-precipitation can occur when nonvolatile impurities are present in the sample matrix, resulting in signal loss of the detected ions [22]. Neutralization of an acidic analyte and any relatively basic interfering substances can occur in the gas phase, therefore reducing the signal of such target analytes [22]. Finally, factors that affect the stability of the generated ions in the gas phase also lead to matrix effects [20].

To obtain a robust LC-ESI-MS method, there is a need to reduce or at least quantitatively compensate for the effects of matrix interferences. Various strategies have been applied to these ends. Conventional approaches such as diluting samples, improving chromatographic selectivity, and utilizing optimal sample preparation procedures are routinely performed. Unfortunately, sensitivity and/or analysis time are usually compromised [23,24]. Some of the newer generation analytical systems can somewhat compensate for these drawbacks [23,25]. Sometimes, commercially available materials such as hybrid zirconia can be utilized for more selective sample preparations [26] or chromatographic separations. But they are useful only in a few specific cases. In situations where matrix interfering components are difficult to remove, compensation approaches are often used to correct for the attenuated signal response resulting from matrix effects. Standard addition, matrix-matched calibration, internal standards, and a more recently

developed correction technique, postcolumn-infused internal standard [27] can be used to compensate for matrix effects. With such approaches, quantitative accuracy is improved at the expense of sensitivity.

Paired ion electrospray ionization (PIESI) was developed for the sensitive analysis of anions and some zwitterions in the positive ESI mode [28–39]. The PIESI mechanism has been studied and has been shown to involve selective association of anions and some zwitterions to an optimal multiply charged ion pairing agent, forming a paired ion of positive charge and enhanced surface activity [40,41]. Anionic analyte LODs are improved one to four orders of magnitude. Other cationic reagents can produce other effects [42,43]. When comparing PIESI and conventional approaches for analysis of actual environmental and/or biological samples, there often appeared to be subjective differences in matrix effects. However to our knowledge, there have been no reports that have systematically evaluated the effect of PIESI on matrix effects using controlled conditions that can be easily reproduced by others. The focus of this study is to evaluate the response of test compounds to specific matrices. Two of the most currently encountered matrices are groundwater and human urine. Five analytes were selected for this study based on the fact that they were previously reported to suffer from matrix effects [44–48]. Analogous parallel studies were done with two different mass spectrometers, a Thermo ESI-linear ion trap (LIT) and a Shimadzu ESI-triple quadrupole (QqQ). These two MS platforms have different ion source configurations and thus can alter the intensities of matrix effects. No sample pretreatment was done except for dilution.

2. Experimental

2.1. Reagents and standards

HPLC-MS grade solvents, methanol and water, were supplied by Honeywell Burdick and Jackson (Morristown, NJ, USA). Ultra-pure water (Milli-Q UV-Plus, Millipore Corp., Bedford, MA, USA) was used for preparation of the artificial matrix solutions. Sodium perchlorate (98% purity), perfluorooctanesulfonate potassium salt (PFOS, $\geq 98\%$ purity), monochloroacetic acid (MCA, $\geq 98\%$ purity), clofibric acid (97% purity) and 2,4-D (99.8% purity) were purchased from Sigma–Aldrich (St. Louis, MO, USA). The structures of these five test compounds were shown in Table S1 in the Supporting Information. Components in artificial matrices described below were all obtained from Sigma–Aldrich. The dicationic ion pairing reagents were synthesized in their bromide form as described previously [28] and were subsequently ion exchanged to their fluoride form prior to analysis to maximize anion/ion pairing reagent complex formation [29]. Their structures, abbreviations and exact masses were listed in Table 1. These reagents also are available from Sigma–Aldrich (St. Louis, MO, USA). Analyte standard solutions were prepared from a stock solution at 1000 ng/mL monthly and were stored at 4 °C in the dark.

2.2. Synthetic matrix preparation

For this project, standard and reproducible matrices were needed. Actual groundwater and urine are neither. Hence the decision was made to use known synthetic matrices that could be exactly reproduced in any laboratory [49]. The PIESI-MS performance was evaluated in two matrices, groundwater and a more complicated urine medium. The recipe for artificial groundwater (AGW) is based on the Edwards Aquifer groundwater located in San Antonio, Texas [50]. This AGW was made up from laboratory-grade reagents (277 mg L⁻¹ calcium carbonate, 20 mL L⁻¹ of 2% nitric acid, 35 mg L⁻¹ sodium sulfate and 90 mg L⁻¹ magnesium chloride

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