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The differences in matrix effect between supercritical fluid chromatography and reversed phase liquid chromatography coupled to ESI/MS

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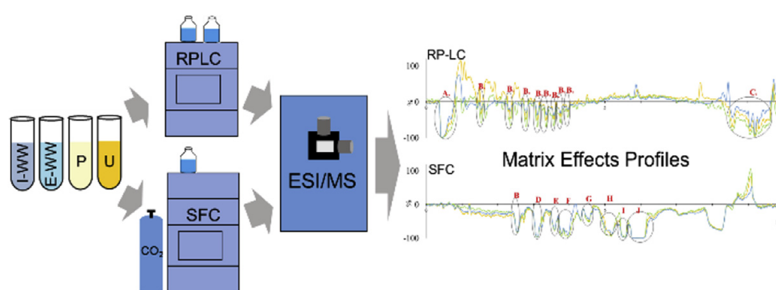
HIGHLIGHTS

- Matrix effects were compared using screening methods with SFC/ESI-MS and RPLC/ESI-MS.
- Blood plasma, horse urine and influent/effluent wastewater were investigated.
- Through the use of post-column infusions, matrix effect profiles were generated.
- Quantitative and qualitative information was compared, interferences tentatively identified.
- Ion suppressions were generally more common for SFC, and enhancements for LC.

GRAPHICAL ABSTRACT



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ABSTRACT

For many sample matrices, matrix effects are a troublesome phenomenon using the electrospray ionization source. The increasing use of supercritical fluid chromatography with CO_2 in combination with the electrospray ionization source for MS detection is therefore raising questions: is the matrix effect behaving differently using SFC in comparison with reversed phase LC? This was investigated using urine, plasma, influent- and effluent-wastewater as sample matrices. The matrix effect was evaluated using the post-extraction addition method and through post-column infusions. Matrix effect profiles generated from the post-column infusions in combination with time of flight-MS detection provided the most valuable information for the study. The combination of both qualitative and semi-quantitative information with the ability to use HRMS-data for identifying interfering compounds from the same experiment was very useful, and has to the authors' knowledge not been used this way before. The results showed that both LC and SFC are affected by matrix effects, however differently depending on sample matrix. Generally, both suppressions and enhancements were seen, with a higher amount of enhancements for LC, where 65% of all compounds and all sample matrices were enhanced, compared to only 7% for SFC. Several interferences were tentatively identified, with phospholipids, creatinine, and metal ion clusters as examples of important interferences, with different impact depending on chromatographic

Abbreviations: E-WW, effluent wastewater; I-WW, influent wastewater; PCI, post-column infusion; PCIMP, post-column infusion matrix profiles; PEA, post-extraction addition.

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technique. SFC needs a different strategy for limiting matrix interferences, owing to its almost reverse retention order compared to RPLC.

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1. Introduction

Matrix effects (ME) constitute a well-known phenomenon, mainly when using electrospray ionization (ESI) connecting liquid chromatography (LC) to mass spectrometry (MS). ME has been called the Achilles heel of LC/ESI-MS, and is generally described as an alteration of the ionization efficiency by co-eluting molecules [1]. The term matrix effects includes both enhancement and suppression of the signal and although the underlying mechanisms are not fully understood, several theories exist [2]. These signal alternations can lead to incorrect quantifications and dramatically higher LODs, since e.g. a severe signal suppression might leave only a few percent of the signal in comparison with that of a neat standard [3]. The most common method to handle ME is through normalization with isotopically labelled internal standards or reduction of the matrix interferences through sample preparation, however with an increase in cost and time consumption. Despite the use of matrix matched calibrators a quantification might be problematic without a suitable internal standard, due to the *relative matrix effect*: i.e., the signal difference between samples containing the same matrix but of different origin, e.g. blood plasma from different individuals [4,5]. An alternation of the chromatographic method to example avoid co-elution of interferences with the analyte could also be an alternative. In multiresidue methods common in e.g. environmental analysis, this might however be problematic due to the high number of compounds, which also may limit the amount of internal standards.

Several sample materials analyzed in e.g. bioanalytical and environmental analysis are known to contain components which often give rise to ME, such as blood plasma, urine, wastewater (WW) and extracts from food, soil and tissues [2,6]. Even if the ME may be decreased with sample preparation, such as extraction or sometimes simply by dilution, its impact on the analytical results has to be tested. This is generally done by an estimation of the matrix effect influence, as recommended when validating analytical methods according to e.g. EMA or FDA guidelines [7,8].

Generally two different methods are used for ME determination, where quantification of ME through post-extraction addition (PEA) is the most common, providing the ME% for a specific compound at its retention time [4]. The second method, with post-column infusion (PCI) of the analyte to determine the effect on signal intensity during the whole chromatographic run, is mainly qualitative [9]. A combination of these two methods, forming the so-called matrix effect profile, has also been described using PCI experiments with standard and matrix injections to determine the ME% for each data point in the chromatogram [10].

The new generation of SFC instruments with wider application possibilities through the use of CO_2 and polar organic solvents and additives has created a new interest for this technique [11]. The electrospray ion source is generally used to combine SFC with MS [12], which also is the interface where ME has its highest impact. Few studies have however been published discussing the matrix effects using SFC/ESI-MS. Most applications have only included ME as a validation parameter, evaluated through an estimation of the ME using PEA [13–15] or PCI [16,17]. To best of the authors' knowledge, two studies comparing ME in SFC and LC-MS have been presented [18,19], developed for doping control of urine samples. In both studies ME was quantified using SRM with a tandem quadrupole mass spectrometer, finding generally lower MEs for SFC-MS than for LC-MS.

The aim of this study was to investigate how the matrix effects in ESI/MS differ between SFC and reversed phase LC, using drug substances, four complex sample matrices and commonly used screening conditions for both techniques.

2. Material and methods

Since the aim was not to develop and validate methods for screening and/or compound quantification, the conditions used were gathered from the literature. For LC, a short UHPLC C18-column was chosen, often used for gradient elution in modern screening methods, with eluents of water and methanol containing 0.1% (v/v) formic acid as primary mobile phase. For SFC, a 2-picolylamine column was chosen, using CO_2 and an 8–45% gradient of the modifier containing methanol and ammonium formate.

The set of drug compounds chosen for this study was selected to include different chemical properties and to ensure a spread in retention times over the chromatographic time scale. Some substances were also included owing to previously observed severe matrix effects in one of the study matrices, e.g. gemfibrozil [20], acetazolamide and miconazole [18].

2.1. Chemicals and reagents

Ammonia solution (4.0 M in methanol), ammonium acetate (Bio-extra ≥98%), ammonium formate (Fluka, LC-MS, ≥99%), formic acid (Fluka, LC-MS grade), methanol (Fluka Chromasolv, LC-MS grade), sodium chloride (≥99.5), acetazolamide (>99%), amiloride hydrochloride-hydrate (≥98%), atenolol (≥98%), carbamazepine (>99%), diclofenac sodium (>99), enalapril maleate (≥98%), fluoxetine hydrochloride (≥99.9%, Riedel-de Haën), gemfibrozil (≥98.5%), hydrochlorthiazide (≥99%), mefenamic acid (≥98%), metoprolol tartrate (≥99%), miconazole (≥99%), propranolol hydrochloride (≥99%), were purchased from Sigma-Aldrich (St. Louis, MO, USA). Acetonitrile (LC-MS grade) was purchased from Fischer scientific (Pittsburgh, PA, USA). Water was obtained from a Milli-Q Q-POD-system from Millipore (Billerica, MA, USA). Carbon dioxide (purity 99.99%) was obtained from Air Liquide (Paris, France).

2.2. Sample preparation

2.2.1. Plasma samples

Pooled human plasma with Na-EDTA (3H Biomedical, Uppsala, Sweden) kept at −80 °C during storage, was thawed in room temperature. The proteins were precipitated by mixing 500 μL plasma with 1000 μL ice cold acetonitrile for 15 s, and centrifugation for 5 min (12 100 g). A portion of the supernatant (1200 μL) was removed and evaporated at 40 °C under a N_2 gas stream. The samples used for SFC analysis were reconstituted in 500 μL acetonitrile:water 75:25 (v/v) and the LC samples in 500 μL water with 0.1% formic acid (v/v) and transferred to vials.

2.2.2. Urine samples

Surplus blank horse urine was obtained from National

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