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The ion suppression phenomenon in liquid chromatography–mass spectrometry and its consequences in the field of residue analysis

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Abstract

During their first period of development, the liquid chromatography–mass spectrometry techniques were met with great enthusiasm from most end-users. An extended application range, the needlessness of derivatisation step prior to injection, the possibility of reduced sample preparation and high throughput analysis were some of the arguments given in favor of these techniques. Few years and more than thousands applications later, more attention is paid to their adverse aspects and limitations, especially regarding the existence of matrix effects. Such problems are well known for many years and may concern various detection techniques. But ion suppression appears as a kind of matrix effect specifically linked to mass spectrometry that probably represents one of the main source of pitfalls in liquid chromatography–mass spectrometry (LC–MS^n). In the actual tendency to promote these techniques for control purposes in the field of residue analysis, it was thought necessary to highlight one of their possible side-effect which may have critical consequences for the analytical results. In this context, the objectives of the present article, which is based on a literature review and additional experiments, were to present the origins and mechanisms of ion suppression, to expose several case studies illustrating its consequences in the field of residue analysis, and finally to propose and comment on some solutions that may overcome this problem.

Keywords: Ion suppression; Mass spectrometry; Liquid chromatography–mass spectrometry; Electrospray ionization; Atmospheric pressure chemical ionization; Residue analysis

1. Introduction

During the first age of the liquid chromatography–mass spectrometric (LC–MS) techniques (1980–early 1990s), a common enthusiasm was shared by the new users of these instruments. One first argument in favor of LC–MS was its suitability for the analysis of compounds presenting incompatibilities with the gas chromatography–mass spectrometry approach (GC–MS), because of their high polarity and/or high mass. Through the atmospheric pressure ionization techniques (API), LC–MS covered this missing wide application domain. A second reason was the needlessness of derivatisation step prior to injection, with advantages in terms of cost and time. One additional argument was the possibility of limited sample preparation and high throughput analysis, considering the LC column only as a loading system. All these arguments participated to the diffusion of these equipments

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in the laboratories, especially in the field of residue analysis.

However, during a second period (1990s-today), some studies started to report some troubleshooting associated to the LC–MS related techniques. For example, a lack of ionization efficiency for non-polar compounds as well as analytical difficulties for highly polar compounds were highlighted by some authors. Thus, a come back to specific derivatisation reactions, or the post-column introduction of solvent modifiers appeared to be helpful in some cases, in order to improve the chromatographic or mass spectrometric behavior of the analytes. A third active research area was related to the gas phase chemistry. Indeed, some observations or experiments demonstrated that gas phase reactions remained partially misunderstood, especially when complex mixtures were involved, with direct consequences in terms of analysis. For instance, analyte transfer from the liquid to the gas phase or the ion stability in the gas phase remained to be fully understood and controlled.

Overall, the main source of analytical problems encountered by LC–MS users corresponded to matrix effects problems. For many years, the composition of a sample extract and the presence of interfering compounds have been recognized to have major influence on the analyte signal, and this observation may concern various detection techniques. But in the specific case of mass spectrometry, the so-called "ion suppression" phenomenon appears as one particular manifestation of matrix effect. This phenomenon represents a main source of pitfall for the analyst, affecting many aspects of the method performances such as detection capability, repeatability, or accuracy. In the clear actual tendency to promote the LC–MS^n techniques for control purposes in the field of residue analysis, it was thought necessary to highlight one of its possible side-effect which may have critical consequences in term of analysis result.

A literature critical review was performed with additional practical experiments. The objectives of the present article were to discuss the current hypothesis advanced to explain the origins and mechanisms of ion suppression, to present several case studies illustrating its consequences in the field of residue analysis, and finally to propose and comment on some solutions that may overcome this problem. One difficulty with this exercise was to give a precise definition of ion suppression. Indeed, other troubles linked to matrix effects could also lead to a disturbed signal and poor repeatability, without being ion suppression (for example a competition for the electronic impact ionization in GC–MS, or isotopic contribution effects in low resolution MS). Therefore, this article will be limited to the commonly admitted definition, i.e. a problem occurring in the early stages of the ionization process of the LC–MS interfaces. Moreover, the field of the present paper is expected to propose complementary data than those usually focusing on pharmacokinetic data in human plasma, with practical experiments from residue analysis at low level in various and complex biological matrices.

2. Theoretical aspects of ion suppression

2.1. Origins of ion suppression

The possible origins of ion suppression are multiple [1]. The main problem source commonly reported is the presence of endogenous substances, i.e. organic or inorganic molecules present in the sample and that are retrieved in the final extract. Among this first group of ion suppressor agents, can be included ionic species (inorganic electrolytes, salts), highly polar compounds (phenols, pigments), and various organic molecules including carbohydrates, amines, urea, lipids, peptides, analogous compounds or metabolites with a chemical structure close to the target analyte one. Finally, a wide range of molecules can lead to ion suppression, especially when they are present in high concentration in the extract and eluted in the same retention window than the analyte of interest.

A second problem source, usually less described, is due to the presence of exogenous substances, i.e. molecules not present in the sample but coming from various external sources during the sample preparation. Among this second group of ion suppressor agents, can be included plastic and polymer residues [2], phthalates, detergent degradation products (alkylphenols), ion pairing reagents [3–5], proton-exchanges promoting agents such as organic acids [5–7], calibration products, buffers, or material released by the solid phase extraction (SPE), LC or GC stationary phases.

2.2. Mechanisms of ion suppression

Different mechanisms have been proposed to explain the ion suppression phenomenon [8,9]. In the case of LC–MS, the main one corresponds to a decrease of the evaporation efficiency due to the presence of matrix components. Indeed, the presence of interfering compounds in high concentration can increase the viscosity and the surface tension of the droplets produced in the electrospray (ESI) or atmospheric pressure chemical ionization (APCI) interfaces, and reduce the capability of the analytes to reach the gas phase. The co-precipitation of the analytes with nonvolatile material such as macromolecules can also limit their transfer in the gas phase. Another proposed mechanism is the competition between analytes and interfering compounds regarding the maximal ionization efficiency of the technique. A total concentration of 10^{-5} M is well known to be the maximal value for an efficient ionization of small organic molecules by ESI [10]. These three first mechanisms occur in the liquid phase. A last possible mechanism occurs in the gas phase, which involves neutralization processes linked to the relative basicity in the gas phase of the analytes and interfering substances, as well as to the stability of the produced ions in the gas phase.

2.3. Consequences of ion suppression

The consequences of ion suppression are numerous, all affecting to a high extent the different aspects of the expected

analytical result. Of course the detection capability is clearly reduced due to the decrease of the analyte signal. The repeatability is also affected, because the degree of suppression may vary in a large extent from one sample to another. Ion ratio, linearity, and quantification, are also affected due to the variability of this unpredictable phenomenon. Another side-effect of ion suppression is the difficulty to perform database searching, because of the modification of the typical mass spectra patterns.

Finally, ion suppression may lead to the nondetection of an existing analyte, to the underestimation of its real concentration, or to the nonfulfillment of the identification criteria, with immediate consequences in terms of false negative (compliant) diagnostic. If affecting the internal standard rather than the analyte, ion suppression may also lead sometimes to an overestimation of the analyte concentration with increased risk of false positive (non-compliant) diagnostic for maximal residue limit (MRL) compounds.

3. Some practical case studies of ion suppression

3.1. A typical alarming situation

After having developed and optimized a purification procedure for a given compound, a specific mass spectrometric measurement for a standard solution submitted to the procedure is expected to produce a satisfying signal, indicating a good recovery of the analyte. Nevertheless, in some cases, the same procedure applied on spiked biological samples lead to abnormally poor signals, and even to the nondetection of the expected signal. In this extreme situation, a first reaction could be to suspect the absence of the analyte in the extract. But using alternative measurement technique on the same extract (ultra-violet, diode array detection, fluorimetry, . . .), the presence of the analyte should be verified. A second reaction could be to extract again the biological sample and to fortify it after purification, just before injection in mass spectrometry. If the expected signal remains very low or undetectable, probably the presence of interfering agents was causing the "ion suppression" phenomenon with a nondetection of the analyte as a consequence.

3.2. An experimental system to identify the problem

The typical experimental system used to evaluate ion suppression in LC–MS is presented in Fig. 1 [6,8]. On one hand, a standard solution containing the analyte of interest is continuously and directly infused into the mass spectrometer interface. On the other hand, a simultaneous LC flow corresponding to pure mobile phase or real sample injection is introduced through a "T"-coupling system. Finally, the resulting signal recorded by the mass spectrometer in full scan mode takes into account the two injected solutions. In case of a standard solution and a pure mobile phase from the LC, the recorded ion current appears more or less constant so no significant variation is noticed on the total ion chromatogram (Fig. 1a). The same observation can be made for one specific extracted ion chromatogram characteristic of the analyte, for example corresponding to the pseudo-molecular ion (Fig. 1b). Indeed in this case, the analyte is not disturbed by any interfering compound. When a blank biological extract is injected onto the LC system, the resulting total ion current increases, due to the new material arriving in the interface to be ionized (Fig. 1c). At the same time, the specific signal of the analyte, that should theoretically remain constant, decreases in certain regions, demonstrating a negative influence of the interfering compounds onto the analyte signal (Fig. 1d).

3.3. Examples of ion suppression investigations

Fig. 2 presents the results obtained with the previous experimental system for the beta-agonist isoproterenol analyzed in bovine meat samples. The sample treatment procedure, which was described elsewhere [11], included a liquid–solid extraction with a methanol-acetate buffer mixture, an enzymatic hydrolysis with *Helix pomatia*, followed by two successive SPE purifications on polymeric stationary phases. As this relatively polar compound elutes early in reversed phase LC system, it may be subjected to matrix interferences caused by the vicinity with the solvent front. The area no 1 (Fig. 2a) corresponds to the direct introduction of the standard solution, with a stable and constant total ion current (TIC). The corresponding mass spectrum (Fig. 2b) shows the presence of the analyte diagnostic ions, i.e. *m*/*z* 212, *m*/*z* 194, and *m*/*z* 152. The area no 2 (Fig. 2a) corresponds to the injection of an extracted blank tissue sample, showing an increase of the TIC because of the new introduced organic material arriving in the interface. The corresponding mass spectrum (Fig. 2c) shows that the intensities of the analyte diagnostic ions clearly decrease, with subsequent increase of the noise and apparition of other ions related to interfering compounds. In the area no 3 (Fig. 2a), the main part of the injected biological extract is eluted and the TIC returns to its initial intensity corresponding to the standard solution, coming back to efficient ionization without any negative disturbance. Fig. 2d presents the extracted chromatograms corresponding to the isoproterenol diagnostic ion *m*/*z* 194, illustrating the ion suppression area where the signal intensity of disturbing material increases while the signal intensity of target analyte decreases. In this example, an estimation of the signal loss between the nondisturbed situation and the maximum of suppression indicates that only 5 % of the real expected signal is detected. Of course such situation could lead to a dramatic underestimation of the analyte concentration if the quantification process is only based on the suppressed target signal, with immediate consequences in term of increased risk of false negative results. Of course the same pitfall occurs if the analyte signal intensity becomes lower than the detection limit.

Fig. 3 presents a second case of ion suppression for the tranquilizers azaperol, azaperon, and the beta-blocker

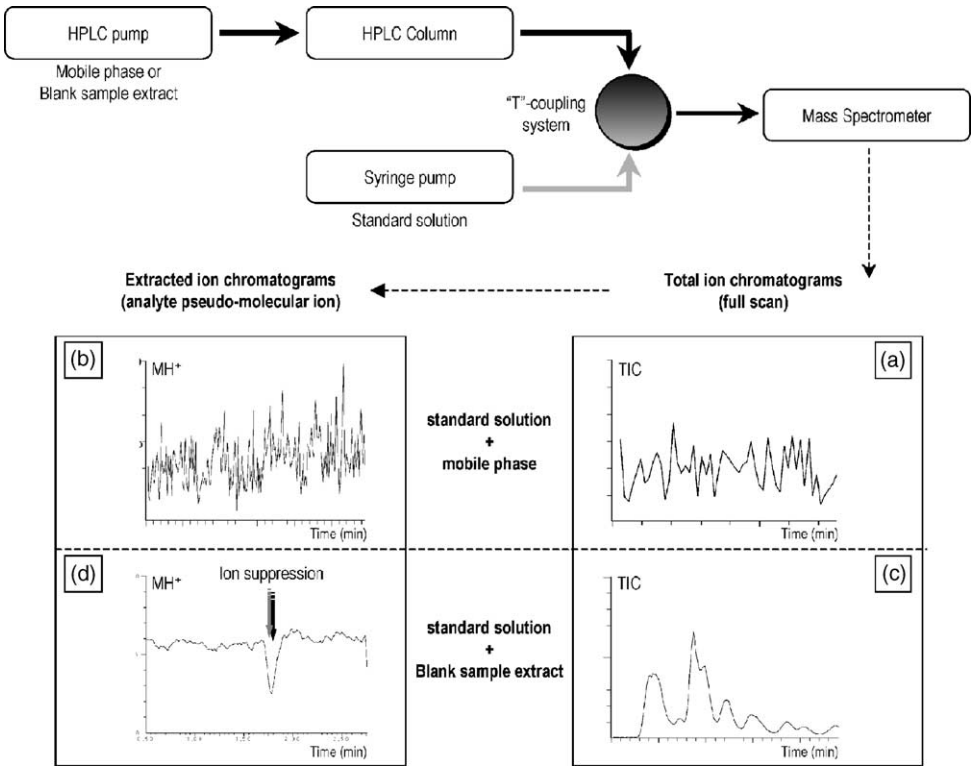

Fig. 1. Typical experiment authorizing the observation of ion suppression. The recorded signal corresponds to a simultaneous introduction of a standard solution (from direct introduction) and a mobile phase or blank sample extract injection (from LC). In the case of a pure mobile phase introduced from the LC, the signal appears constant (a,b). In the case of a biological extract, the TIC increases (c) but the specific trace of the analyte may be suppressed (d) due to interferences entering the interface.

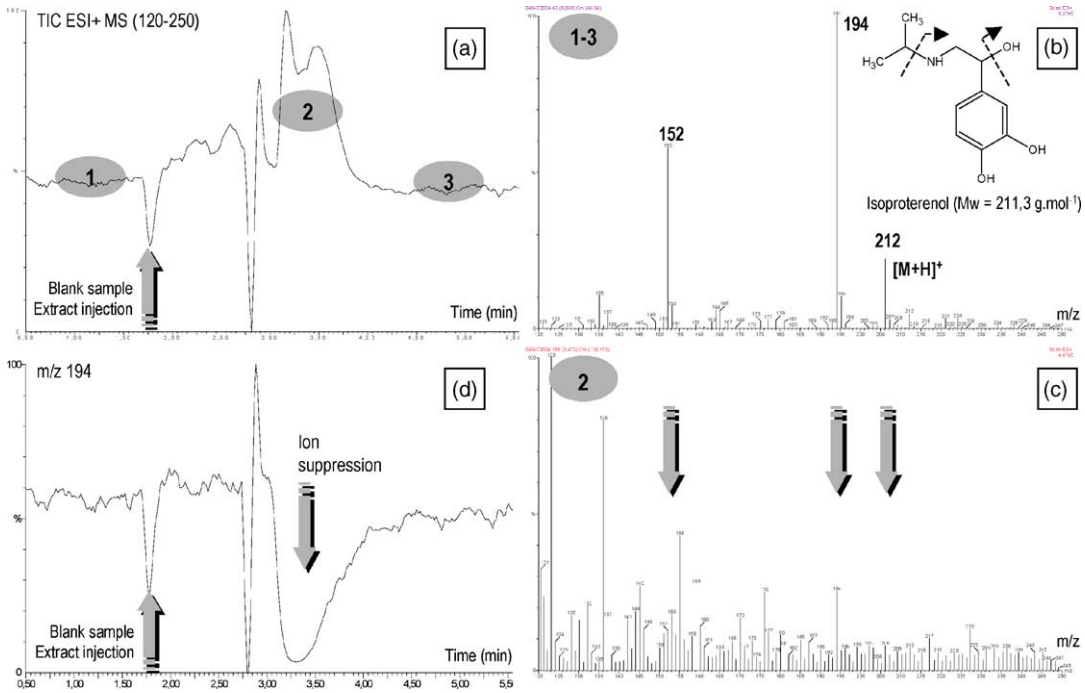

Fig. 2. A case study of ion suppression for the beta-agonist isoproterenol in meat sample extract: (a) total ion chromatogram recorded before (area 1), during (area 2) and after (area 3) injection of a blank muscle extract; (b) mass spectrum observed during the nondisturbed areas 1 and 3; (c) mass spectrum recorded during the disturbed area 2; (d) extracted ion chromatogram corresponding to the isoproterenol ion *m*/*z* 194 revealing the area of ion suppression.

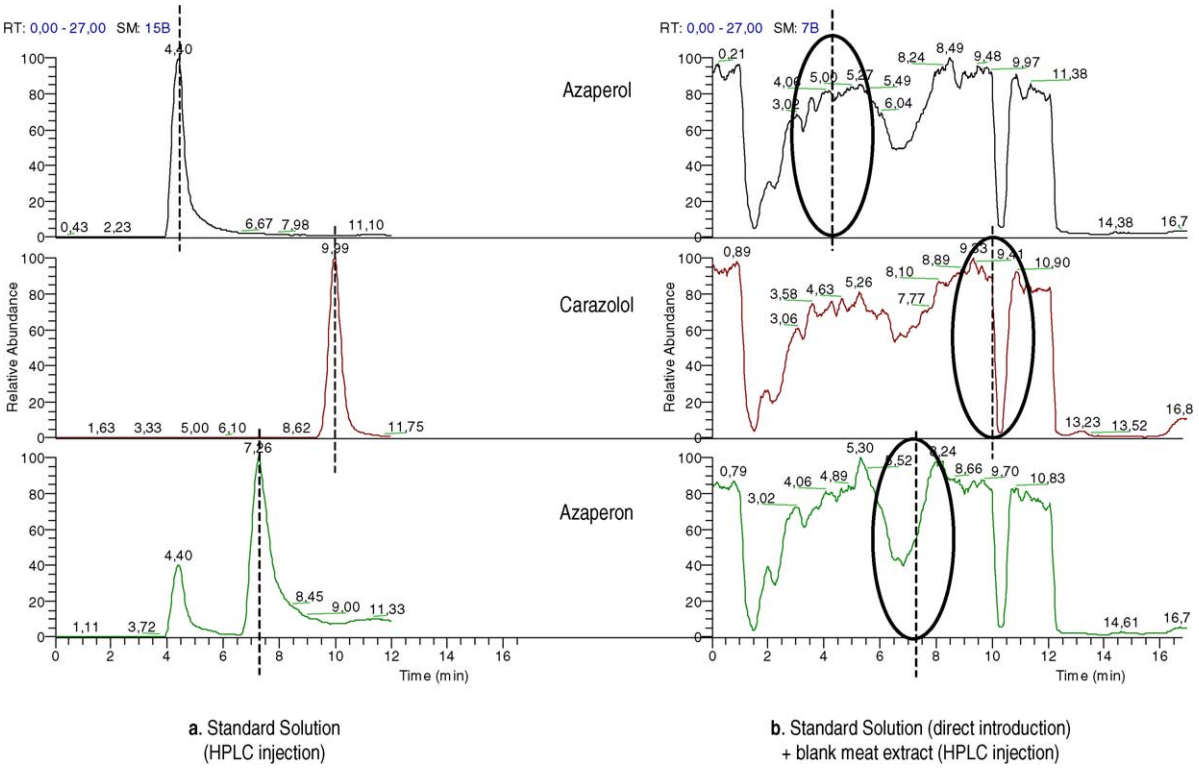

Fig. 3. A case study of ion suppression for the tranquilizers azaperol, carozolol and azaperon in meat samples: (a) diagnostic ion chromatograms obtained for a classical LC injection of standard solutions; (b) diagnostic ion chromatograms obtained for a standard solution. No significant suppression is observed for azaperol, but severe suppression occurs in the retention time windows of carozolol and azaperon.

carozolol, also analyzed in meat samples. These analytes were extracted from meat samples using acetonitrile. The clean-up consisted of a solid phase extraction. The evaporated eluate was reconstituted in mobile phase prior to injection. Using the previously described experimental strategy consisting in the simultaneous injection of a standard solution (from direct introduction) and a blank meat extract (from LC), no significant suppression was observed for the diagnostic signal of azaperol near its expected retention time (Fig. 3b-up). But a severe ion suppression appeared for carozolol and azaperon near their respective retention times (Fig. 3b-midle and -down). This example illustrated that ion suppression caused by interfering compounds may occur on various regions of the chromatogram, all along the LC run. Consequently, such an experiment to evaluate the ion suppression should be performed during method development and validation in order to prevent some problems regarding repeatability or quantification.

4. Possible action levels to overcome ion suppression

4.1. The measured signal (modify mass spectrometric conditions)

The first action taken to overcome the ion suppression problem should be to modify the mass spectrometric conditions if possible. This solution should be advantageous because it does not require any change in the rest of the developed analytical procedure (sample preparation and chromatographic conditions). Indeed, the occurrence of ion suppression may differ between different ionization techniques (ESI, APCI, APPI), ionization modes (positive or negative), or between equipments with different source design [2,4,12–14].

Historically, some authors reported that ESI was more subjected to ion suppression. More recently, other authors estimated that APCI was more affected by this phenomenon. Actually, the two techniques are considered as equally affected, because in both cases the nature and the composition of the mobile phase are known to influence to a high extent the ionization process. Moreover, because the ionization occurs in liquid phase for ESI and in gas phase for APCI, the mechanisms of ion suppression should be different for both techniques. APPI is a more recent technique and consequently less investigated in term of ion suppression [15]. But theoretically, ion suppression can also occur with this technique, due to the role of the liquid phase in the ionization process. However, because this technique is particularly adapted to non-polar compounds, the molecule susceptible to interfere with the analyte of interest are probably different than in ESI or APCI, for which the problem is mainly due to polar compounds. Moreover, the mechanisms of ion suppression in APPI may be certainly different than in ESI or APCI, because of a completely different ionization

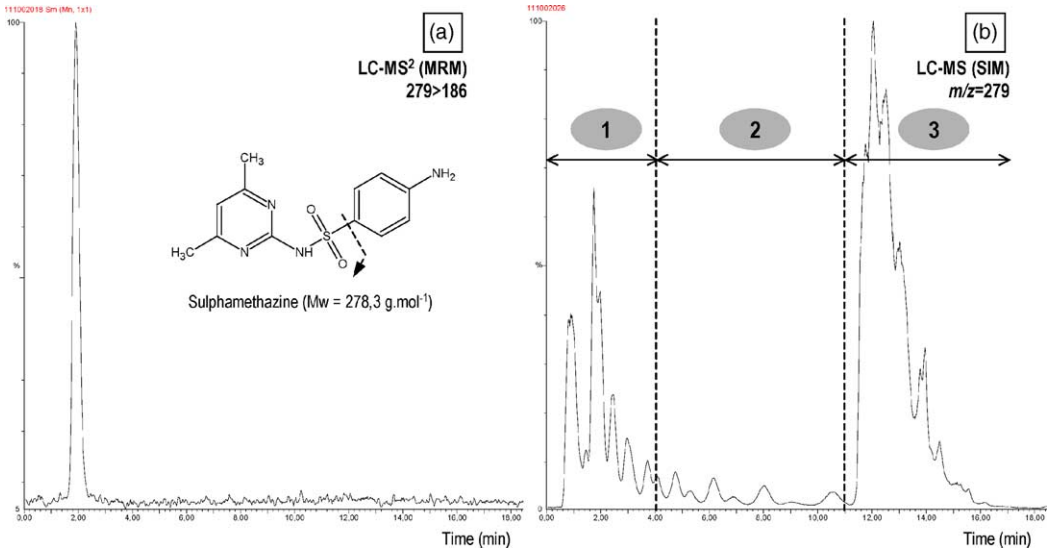

Fig. 4. LC–MS^2 (MRM) and LC–MS (SIM) diagnostic ion chromatograms of sulfamethazine obtained for a spiked muscle sample. The highly specific acquisition modes can make the interfering compounds undetectable, but they do not suppress them. The areas more subjected to interferences and ion suppression are the solvent front (1) and the end of elution gradient (3). The target analytes should be preferably eluted in the area (2).

processes involved. Proton affinities of both the analytes and interfering compounds are probably crucial on this point of view.

Regarding the ionization polarity, the negative mode is usually considered as more specific, and consequently less subjected to ion suppression. Indeed, the number of compounds giving a response in the negative mode is clearly lower than in the positive mode. Consequently, the aspect of the ion chromatograms and the signal to noise ratio are usually better in the negative mode. Regarding the influence of the source geometry, a linear transfer line between the capillary and the sample cone was sometimes described as more disturbing than an orthogonal design in term of ion suppression. This observation is certainly justified for matrix effect in general, because an orthogonal design may improve the transmission of the ions of interest with simultaneous discarding of unwanted species susceptible to interfere with the analytes. But considering that ion suppression occurs in the early stages of the ionization process, i.e. before or immediately after the transfer of the analyte in the gas phase as ionic species, the influence of the later stages, i.e. the transfer of the produced ions in the analyzer should have in fact minor influence. For the same reason, it appears not justified to claim that a triple quadrupole or an ion trap is more subjected or sensitive to ion suppression. Indeed, because the difference between the two instruments concerns the mass filters and not the interface, the potential problems occurring during ionization such as ion suppression should be similar in both cases. However, the two instruments should not be equally sensitive to other matrix effects leading to problems in term of signal or ion ratio stability. Finally, special attention should be paid to this possible confusion between matrix effect in general and ion suppression in particular.

4.2. The quantification process (use appropriate internal standard)

The previously described case studies demonstrated that an identification and quantification processes only based on the target analyte signal can be very critical in case of ion suppression. Of course, most laboratories do not use such absolute response, but a relative response reported to an internal standard (IS). Moreover, a systematic use of spiked extracted samples for calibration curves instead of standard solutions is clearly preferable. However, a main characteristic of ion suppression is a high variability from one sample to another with different influences from one compound to another. Consequently, a differential suppression between the analyte and the IS may lead to critical situations. If ion suppression mainly affects the analyte rather than the IS, this could lead to underestimation of the analyte real concentration, with immediate consequences in term of false negative conclusion. At the opposite, if ion suppression mainly affects the IS rather than the analyte, this could lead to overestimation of the analyte concentration, with consequences in term of false positive results.

An obvious solution to overcome this problem is to use adequate internal standard, in order to balance the disturbance of the analyte signal by an equivalent disturbance on the internal standard [16–18]. The best way to achieve this goal should be to get available analogous compound presenting a chemical structure and a retention time as close as possible to those of the analyte. For this purpose, ^{13}C- or ^{2}H-labelled corresponding molecules usually permit to reduce to a great extent the signal variability observed for the analyte and consequently to improve the repeatability of the measurement. As an example taken from a method developed by the authors for

corticosteroids in tissue samples, the signal intensity variability obtained for triamcinolone acetonide in 20 spiked muscle sample replicates was reduced from 32.6% using the IS fludrocortisone to only 5.7% using triamcinolone acetonide-d6. Of course in this example, the advantage of the deuterated IS is not limited to balance the eventual problems occurring during ionization, but to all the sample preparation procedure. A second example, from Kitamura et al. [16] demonstrated the real benefit to force the IS and the analyte to be eluted at the same time in order to have similar behavior during ionization. These authors showed that by modifying their LC conditions in order to adjust the retention factors of their analyte (3′-C-ethynyl-cytidine) and IS (3′-C-ethylcytidine), the variability of the analyte relative response, observed for five spiked rat plasma samples, was reduced from 16.3 to 3.7%. In this second example, this observation was clearly explained by similar conditions around the analyte and IS during the ionization process because the two compounds reached the interface simultaneously.

4.3. The chromatographic system (improve retention and separation)

Another reason to modify the elution conditions may be to shift the retention time of the analytes of interest far away from the area affected by ion suppression [13,19,20]. To illustrate this, Fig. 4 presents two ion chromatograms obtained for the antimicrobial sulfamethasine analyzed in pork muscle samples, and measured using either LC–MS/MS or LC–MS acquisition mode. On the highly specific trace obtained in LC–MS^2 with MRM acquisition mode (Fig. 4a), the presence of the analyte was unambiguously revealed because of the very clean aspect of the chromatogram. But on the less specific trace obtained in LC–MS with SIM acquisition mode (Fig. 4b), the presence of interfering compounds clearly appeared, making the interpretation and the identification of the target molecule more delicate. This example illustrated that if the highly specific acquisition modes can make the interfering compounds undetectable, they do not suppress them. Special attention should be paid for analytes eluting in the solvent front (where all highly polar and nonretained compounds are eluted) or during the end of the elution gradient (washing step of the analytical column where the strongly retained compounds are eluted), which are two areas more affected by interferences and then to ion suppression. Consequently, it can be recommended when possible to adjust the retention factors of the analytes in order to elute them between these two regions.

4.4. The sample preparation (improve purification and clean-up)

The previously described action levels should permit to balance the effects – or minimize the consequences – of ion suppression, but they do not eliminate the risk as the cause is not treated. The only way to definitively circumvent this problem remains to improve the sample preparation and purification, in order to limit the presence of interfering compounds in the final extract. Numerous authors demonstrated the evidence of such approach. Therefore, it should be suggested to check the matrix effects resulting from different sample treatment procedures systematically. In other word, the usual tendency to consider the recovery of the target analyte as a main performance indicator should be moderated by the necessity to evaluate also the method efficiency in terms of removing interfering compounds. For example in urine, some highly concentrated endogenous compounds such as creatinine [21] or enterolactone were demonstrated to induce severe ion suppression for hormonal residue analysis and should be removed using appropriate analytical strategy. There is no universal strategy, but only solutions case by case for each analyte/matrix combination. One approach presenting the advantage to require no consistent effort should be a dilution of the sample or a reduction of the injected volume. However, these solutions clearly appears inappropriate for trace analysis when very low detection limits are expected to be achieved. Indeed, a dilution by factors 2–5 may be critical for the analyte present at ultra-trace level and without any effect on an interfering substance present in high concentration. So improve the sample purification is usually to be preferable despite requiring more work. Various authors reported some analytical developments related to residue analysis for which different purification methods were tested [20–25], for example LLE, MIPs, or SPE (C_{18}, polymeric, ion exchange, . . .). The final choice depending on each specific application, but also considering the mode of utilization of the technique. Consequently, one recommendation should be to perform the experimental assay permitting to evaluate ion suppression as an additional parameter during the method development when LC–(API)–MS techniques are used. Finally, all theses studies demonstrated the limits of the LC–MS techniques in case of insufficient sample preparation prior to measurement.

5. Conclusion

After a first period of development mainly characterized by several seductive commercial arguments and a great enthusiasm from most end-users, the liquid chromatographic–mass spectrometric equipments have found a place of choice in many laboratories. Their utilization in the field of residue analysis was mainly motivated by recognized advantages in term of sensitivity and specificity, which ensure high performances for unambiguous identification and quantification. However, the existence of disturbing matrix effects are today highlighted. Among those ion suppression represents one of the main source of pitfalls encountered with these techniques. The origins and mechanisms of ion suppression were briefly presented, showing the need for an increased attention for the quality and purity of the injected extracts (endogenous interferences) but also of all the analytical material and consumables (exogenous interferences). Several case studies were

given, demonstrating the possible consequences of ion suppression in the field of residue analysis, with immediate influence in term of false negative or false positive results, both for banned and MRL substances. Finally, possible solutions to overcome this problem were proposed and commented, some of them trying to balance the effect or minimize the consequences of ion suppression. With the final conclusion that only a combination of judicious internal standard choice and deep sample purification may permit to ensure optimal performances in term of repeatability and quantification.

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