11-2019

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Recommended Citation

Kukowski Klara, Gysbers Brianna, Stephen Fisher, et al.. "Optimization of Electrospray Ionization for Liquid Chromatography Time-of-Flight Mass Spectrometry Analysis of Preservatives in Wood Leachate Matrix" (2019). *Chemistry Faculty Publications*. 21.
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Optimization of electrospray ionization for liquid chromatography time-of-flight mass spectrometry analysis of preservatives in wood leachate matrix

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Abstract

Triazoles and 3-iodo-2-propynyl butylcarbamate (IPBC) are commonly used wood preservatives active against a wide range of fungi and bacteria. As they are prone to leaching, their amounts need to be monitored by the industry to determine preservative loss from the products and for environmental assessment. Therefore, a liquid chromatography - electrospray - time-of-flight mass spectrometry (LC-ESI-TOFMS) method was developed and optimized for simultaneous quantification of triazoles and IPBC in aqueous wood extracts, specifically wood leachate.

Analyte pre-concentration on a solid-phase extraction cartridge prior to the analysis yielded > 94% recoveries. ESI method parameters (e.g., solvent system, electrolyte type, electrolyte concentration, capillary, and fragmentor voltages) were selected based on an initial screening followed by an in-depth optimization via design of experiments. The optimal conditions employed an acetonitrile-water solvent system with 1.7 mM ammonium acetate, capillary voltage of 4350 V, and fragmentor voltage of 115 V. The developed method was applied to industrial wood leachate samples and the matrix-affected limits of detection were found to be 1.2–1.5 $\mu\text{g}\cdot\text{L}^{-1}$ with interlay repeatability being <7%.

Keywords

fungicides; electrospray ionization; wood leachate; liquid chromatography; time-of-flight mass spectrometry; design of experiments, triazoles, IPBC

Graphical Abstract

1. Introduction

As wood is known to be susceptible to biological attacks caused by fungi and bacteria, it is commonly treated with organic biocides to enhance its durability. Many organic preservatives are only effective against a specific class of microorganisms; nonetheless, synergistic effects were reported for a group of triazole fungicides, helping to overcome this selectivity [1, 2]. Triazoles were first introduced to the market after the 1980s [3], and are now among the most commonly used fungicides in the wood industry [4-6]. Frequently used representative compounds include tebuconazole (TAZ), propiconazole (PAZ), and azaconazole (AZA). Aside from formulations containing mixtures of these triazoles, they are often enriched with 3-iodo-2-propynyl butylcarbamate (IPBC), which is both an insecticide and antimicrobial agent, to further enhance the efficacy and broaden the spectrum of activity.

As triazoles and IPBC are prone to leaching, their amounts in wood leachate should be regularly monitored to assess the losses from treated products and to determine the potential for environmental contamination. The American Wood Preservers Association (AWPA) method [7] for triazole determination in waterborne solutions utilizes liquid chromatography coupled to ultraviolet detection (LC-UV) with no prior sample manipulation resulting in higher limits of detection (LODs) than those achievable either by mass spectrometers (MS), or by employing sample pretreatment. Even though sensitive LC-MS methods for determination of fungicides in aqueous samples were developed as discussed further below, to our knowledge, they have neither simultaneously targeted triazoles and IPBC, or have not been optimized for wood leachate matrix.

Wood leachate is a highly variable chemical matrix changing with respect to wood age, location, and environmental conditions [8]. The complexity as well as the difference in polarity and structure of its components complicate the direct and simultaneous analysis of preservatives in wood leachate. Therefore, a sample purification step, such as solid-phase extraction (SPE), prior to LC-MS analysis is essential to achieve good accuracy, repeatability, low LODs, but also to extend column lifespan. Furthermore, SPE prior to LC-MS aids the pre-concentration of analytes onto the cartridge, since their amounts in industrial wood leachate, although significant, may be near the method LODs.

As a result, SPE has been commonly employed for triazole determination in various matrices, such as water [9-13], beverages [14, 15], food and soil [16-22], wood [23, 24], and animal tissue [25]. However, SPE techniques targeting only

triazoles may not be applicable to IPBC isolation as its chemical structure greatly differs from that of triazoles. Only a few SPE methods have been developed targeting both triazoles and IPBC [24, 26, 27], often employing an HLB cartridge. Since HLB is a reversed-phase sorbent composed of two monomers, hydrophilic N-vinylpyrrolidone and lipophilic divinylbenzene, it is suitable for the retention of a wider range of analyte polarities.

The majority of published LC methods developed for triazole and/or IPBC determination in aqueous samples used either MS [11, 22, 25, 26, 28-35] or UV detection [23, 36-38]. Quantification using MS was mostly accomplished with electrospray tandem mass spectrometers (ESI-MS/MS) to achieve limits of quantification (LOQs) in the sub-ppb levels, however, none of these methods were developed specifically for wood leachate matrix [11, 22, 25, 26, 28, 30-35]. As part of these studies, ESI-MS/MS parameters were typically optimized (e.g., ion transitions, capillary and collision voltages), but the solvent and electrolyte system either did not appear to be evaluated, or was not reported. Yet, the composition of LC mobile phase and the choice of electrolyte and its concentrations has a significant impact on ESI ionization efficiency, and hence the LODs [39]. Finally, only a couple of triazole quantification methods for aqueous samples have been developed on a non-tandem MS, such as time-of-flight MS (TOFMS), but they did not target IPBC [40, 41].

Therefore, a method for simultaneous determination of triazoles and IPBC in wood leachate using SPE followed by LC-ESI-TOFMS was developed in this study combining the advantages of the earlier published methods. Analyte pre-

concentration was achieved using an SPE-HLB cartridge prior to the analysis, exhibiting high fungicide recoveries. The method conditions (e.g., solvent system, electrolyte type, electrolyte concentration, capillary and fragmentor voltages) were selected based on an initial screening followed by an in-depth optimization via response surface design. Matrix-affected LODs and LOQs were also assessed. Finally, the developed method was applied to real-world industrial wood leachate samples.

2. Materials and Methods

2.1 Chemicals and Reagents

Analytical standards, TAZ, PAZ, AZA, IPBC, and hexaconazole (HAZ), which was used as an internal standard (IS), were of > 99% purity and purchased from Sigma-Aldrich (St. Louis, MO, USA). Solvents (e.g., acetone, methanol, and acetonitrile of LC or GC grade) and electrolytes (e.g., acetic acid, formic acid, ammonium acetate, and ammonium formate) were obtained from Fisher Scientific (Pittsburgh, PA, USA). Water was purified using a DirectQ Millipore system (Billerica, MA, USA). SPE PRiME HLB cartridges (3 cm³, 60 mg sorbent) were purchased from Waters Corporation (Milford, MA, USA).

2.2 Wood Matrix Extract for SPE Validation

An aqueous wood extract was prepared by Soxhlet extraction of pine wood with acetone to obtain a highly concentrated matrix solution, with subsequent evaporation of the acetone followed by re-dissolution of the wood matrix

components in water. Specifically, untreated ponderosa pine samples stored under standard conditions of an air-conditioned building (22 ± 2 °C, ambient pressure and ca. 50% relative humidity) were sheared with a hammer and knife into smaller pieces to allow for an exhaustive extraction, which was carried out for 16 hours using a Soxhlet apparatus with 130.0 mL of acetone [42]. The wood extract was then evaporated to dryness under a gentle stream of nitrogen, re-dissolved in water, and filtered through 0.2 µm syringe filters. The resulting aqueous wood matrix extract was spiked with a fungicide stock solution in methanol (MeOH) to achieve the desired analyte concentration (~20 ppm, w/v) in 10% MeOH. This 10% MeOH wood extract was only used to evaluate the SPE method as it represented the worst-case scenario for wood leachate with each aliquot (0.5 mL) containing matrix from 0.5 g of wood.

2.3 Industrial Wood Leachate Samples

Industrial leachate samples were prepared at a Marvin Windows and Doors facility (Warroad, MN, USA) by direct aqueous leaching of wood preserved with fungicides. Specifically, ponderosa pine wood sections (1.5 x 1.5 x 8") were dip-treated with a commercially available Woodlife 111 solution (containing 0.22% of TAZ and PAZ, made by Kop-Coat, Inc., Pittsburgh, PA, USA), dried and painted white (aqueous white paint manufactured by The Valspar Corporation, Minneapolis, MN, USA). Next, ten wood sections were placed on a raised platform in Rubbermaid roughneck totes (18-gallon volume) under a flowing, recirculating water irrigation system. The sections were laid horizontally on the platform and water was sprayed in a 90° angle (thus exposing both the radial and tangential

wood surface). Wood sections were exposed to 11.3 L of water per week for a total of four weeks. A control experiment involved the same setup using 10 wood sections that were not treated with preservatives. Because this wood leachate did not contain any fungicides, it was used for determining the matrix-affected LOD and LOQ.

2.4 Sample Purification

To achieve the retention of triazoles and IPBC on the solid phase while eluting interfering water-soluble components, reversed-phase PRiME HLB SPE cartridges were employed with the protocol details and recoveries from wood extract shown in Table 1. For the analysis of industrial leachate, 3 mL of aqueous samples were loaded onto the HLB column. The fungicides collected in ACN with 2% ammonium hydroxide solution were concentrated down to 0.3 mL under a gentle stream of nitrogen, mixed with 0.7 mL of water, and spiked with IS prior to the LC-ESI-TOFMS analysis. Further details can be found in Supplementary Materials.

Table 1. The SPE-PRiME HLB protocol developed for retention of fungicides present in wood leachate.

PRiME-HLB SPE protocol	
Sample load	0.5 mL of wood matrix extract in 10% MeOH or 3 mL of industrial wood leachate
Matrix wash	3 mL 10% MeOH solution
Analyte collection	3 mL ACN with 2% ammonium hydroxide

SPE-PRiME HLB Recoveries

TAZ	PAZ	AZA	IPBC
96 ± 4%	102 ± 3%	102 ± 2%	94 ± 5%

2.5 ESI-TOFMS Optimization

The ESI-TOFMS optimization using flow injection analysis (FIA) consisted of two parts. At first, an initial screening was performed to select the suitable solvent system, e.g., ACN or MeOH, and electrolyte (Table 2) using TAZ, and IPBC (screened separately, with the total of 64 experiments). Based on preliminary screening, a thorough optimization of ESI-TOFMS conditions for TAZ, PAZ, and IPBC was performed using a response surface design, to assess the expected curvature. The ACN-water system with ammonium acetate as an electrolyte were employed based on the screening results.

As in our previous studies [39, 43], all optimization experiments were conducted using a FIA, where samples containing fungicides and the electrolytes (concentration range 4–400 mM) in the evaluated solvent system (MeOH/ACN and water 50:50, v/v) were injected into a mobile phase flow (MeOH/ACN and water, 50:50, v/v). The electrolyte concentration in the sample was four times higher than the desired concentration in the ESI chamber (i.e., 1–100 mM) to account for the dilution in the mobile phase (i.e., 50 μ L sample injection into 0.2 mL·min⁻¹ flow).

The final concentration of fungicide standards in the ESI chamber was ~10 ppm (w/v).

Table 2. ESI-TOFMS conditions optimized, for details see Supplementary Tables 1 and 2.

Screening conditions		
evaluated in both MeOH-water and ACN-water solvent systems		
Experiment #	Electrolyte	Conc. [mM]
1	formic acid	1
2		10
3		100
4	ammonium formate	1
5		5
6		10
7	ammonium formate + formic acid (50:50, v/v)	1
8		10
9	acetic acid	1
10		10
11		100
12	ammonium acetate	1
13		5
14		10
15	ammonium acetate + acetic acid (50:50, v/v)	1
16		10
Response surface design		
Factor	Low level	High level
Electrolyte concentration [mM]	2.5	5
Capillary voltage [V]	4500	5000
Fragmentor voltage [V]	125	150

2.6 Instrumentation

Both FIA and LC-ESI-TOFMS analyses were conducted on an Agilent 1100 LC coupled to a high resolution TOFMS G1689A Series 6200. LC separations were performed using an Agilent Eclipse Plus C18 150 mm × 2.1 mm reversed-phase LC column with 3.5 μm particle size. The flow rate was 0.2 mL·min⁻¹. The optimized LC method employed a solvent system consisting of A: 5% ACN in water with 1.7 mM ammonium acetate and B: ACN with 1.7 mM ammonium acetate. The gradient elution was evaluated starting at 20, 30, 40, or 50% ACN, but the final program began at 30% B and increased to 55% B in 21 min followed by a further increase to 65% B in 5 min (time 26 min). It reached 90% B in 1 min (time 27 min) and was held at 90% B for an additional 1 min (time 28 min). The %B was then decreased back to 30% in 1 min (time 29 min) and held there for an additional 11 min to provide sufficient time for column equilibration. The total analysis time was 40 min. During the analysis, the flow was first diverted into a waste container for the initial 7 min, and only then directed into the TOFMS to minimize the ESI chamber contamination of with both salts and early eluting species. The column oven temperature was set to 30 °C and the injection volume was 50 μL . ESI was performed in positive mode with drying gas (N_2) set to 350 °C at a flow rate of 12 L·min⁻¹, and the nebulizer gas (N_2) pressure set to 25 psig. The capillary and fragmentor voltages were 4350 V and 115 V, respectively.

2.7 Data Processing

The LC-ESI-TOFMS data were processed using Analyst QS 1.1 (Applied Biosystems) and MassHunter Workstation Quantitative Analysis B.04.00 (Agilent Technologies). Fungicides were identified based on their retention times and mass spectra matching those of individual standards. Quantification employing an IS method was accomplished by integrating the extracted ion current (EIC) chromatograms of the corresponding protonated molecular ions $[M+H]^+ \pm 0.03$ m/z ; 308.153 for TAZ, 342.077 for PAZ, 300.030 for AZA, 281.999 for IPBC, and 314.082 for HAZ.

Minitab 16.1.1 was used for statistical analysis. DOE response surface design was employed for the optimization of ESI-TOFMS ionization, where factors and interactions were considered significant when the p -value was lower than 0.10 (i.e., 90% confidence level). Response surface design methodology is routinely used when curvature in the response surface is suspected, and it was previously reported as a systematic approach for the optimization of analytical methods [44, 45]. A response surface optimizer function was further employed to find the settings yielding the highest MS response of all fungicides. By selecting a target value (i.e., MS peak area), Minitab calculated an optimal solution based on the conducted experiments.

Instrumental and matrix-affected LODs and LOQs were calculated from the calibration curves generated using a least square linear regression. Only the calibration points that were within one order of magnitude of the LODs were used.

The calculation was based on the following equations: $LOD = 3.3 \times s_y/m$ and $LOQ = 10 \times s_y/m$, where s_y is a standard error of the predicted y-value for each x-value and m is a slope of the calibration curve. To calculate matrix-affected LODs and LOQs, the control industrial wood leachate (i.e., generated from untreated wood; see Section 2.3) was purified using the developed SPE protocol (e.g., 3 mL of leachate per calibration standard). Next, it was evaporated to 0.3 mL, mixed with 0.7 mL of water, and spiked with IS and fungicides in the concentration range of one order of magnitude of LOD.

3. Results and Discussion

3.1 Screening of ESI Conditions

The organic solvent selection did not seem to affect the fungicide MS response as both ACN and MeOH yielded similar results (data not shown). Thus, ACN was selected since it was also employed to elute fungicides from the SPE-HLB cartridge and provided a lower backpressure for LC analysis. In addition, an ACN-water system exhibits a lower UV cut-off wavelength, which is desirable as many LC-MS instruments offer a secondary UV detection.

On the other hand, the selection of electrolyte and its concentration had an apparent impact on the fungicide ionization (Figure 1). For all conditions, the TAZ response was ~2x higher than the IPBC response, indicating a lower ionization efficiency for the latter. For both TAZ and IPBC, the MS response was higher when acetic acid or ammonium acetate were used compared to formic acid or ammonium formate. Overall, ammonium acetate appeared to be the best

compromise, yielding an effective ionization of IPBC as well as sufficient ionization of triazoles.

Figure 1. Impact of electrolyte type and its concentration in an ACN-water system (50:50, v/v) on TAZ (**A**) and IPBC (**B**) ESI-TOFMS responses.

3.2 Response Surface Design Optimization of ESI-TOFMS

A detailed optimization of ESI-TOFMS conditions was performed using an ACN-water solvent system with ammonium acetate as an electrolyte (selected based on the screening experiments) to study the interaction of ammonium acetate with the capillary and fragmentor voltages. In general, the electrolyte concentration ($0.005 \leq p \leq 0.090$) and the capillary voltage ($0.065 \leq p \leq 0.085$) were the two most influential factors for TAZ and PAZ detection (see details in Supplementary materials). By contrast, IPBC response was significantly impacted by the electrolyte concentration and the fragmentor voltage (both yielding $p = 0.000$). The response surface plots constructed using these two factors for each fungicide were found to be curved (Figure 2), thus demonstrating the need for a simultaneous optimization of the electrolyte concentration and ESI voltages.

For triazoles, the conditions yielding the highest responses included ammonium acetate concentrations below 2 mM and capillary voltages below 4450 V or above 5150 V. For IPBC, the optimum conditions were ammonium acetate concentrations below 3 mM and fragmentor voltages below 133 V. Also, as observed previously, IPBC exhibited the lowest MS responses compared to TAZ and PAZ. The optimal ESI conditions (i.e., maximizing response for the three analytes simultaneously using the same factor levels) were found to be 1.7 mM ammonium acetate, a capillary voltage of ~ 4350 V, and a fragmentor voltage of ~ 115 V.

A

B

C

Figure 2. Surface plots for TAZ (**A**), PAZ (**B**), and IPBC (**C**) constructed using the two most influential ESI factors based on the peak areas obtained for $[M+H]^+$ ions.

3.3 Matrix-Affected LOD and LOQ

Instrumental LODs and LOQs (Table 3) were determined using fungicide standards in pure solvents, while matrix-affected values were calculated from standards spiked into a SPE-purified industrial wood leachate (i.e., control leachate, Section 2.3). The matrix-affected LOQs for triazoles ($\leq 1.4 \mu\text{g}\cdot\text{L}^{-1}$) were considered satisfactory since they fell in between those reported by Robles-Molina *et al.* (LOQs $< 10 \text{ ng}\cdot\text{L}^{-1}$) [40], and Amelin and Andoralov (LOQs of $60 \mu\text{g}\cdot\text{L}^{-1}$ for TAZ) [41], and could be further lowered by pre-concentrating larger sample volumes on the SPE-HLB cartridge. Also, the previously published LOQs were obtained for aqueous samples not containing wood leachate matrix, they were not measured on LC-ESI-TOFMS, and the methods for which LOQs were determined did not aim for simultaneous IPBC and triazole quantification.

Table 2. ESI-TOFMS instrumental and matrix-affected LODs and LOQs for triazoles and IPBC expressed in concentration of $\mu\text{g}\cdot\text{L}^{-1}$.

	Instrumental [$\mu\text{g}\cdot\text{L}^{-1}$]				Matrix-affected [$\mu\text{g}\cdot\text{L}^{-1}$]			
	AZA	IPBC	TAZ	PAZ	AZA	IPBC	TAZ	PAZ
LOD	0.1	0.2	0.2	0.2	0.4	0.5	0.5	0.4
LOQ	0.4	0.7	0.7	0.6	1.2	1.5	1.4	1.3

3.4 Method Application to Industrial Wood Leachate

The developed method was employed for quantification of fungicides in an industrial wood leachate received from Marvin Windows and Doors. A total of four samples were analyzed (i.e., leachate from weeks 1–4) after their pre-concentration on SPE-HLB cartridges. While TAZ and PAZ were detected in all industrial samples, IPBC was not found. This

was consistent with our previous observation [42], when a significant loss of IPBC was observed with light and moisture being the main factors (**Figure 3**). Also, this specific wood treatment did not contain AZA or HAZ.

Figure 3. LC-ESI-TOFMS chromatograms of industrial leachate samples analyzed either directly (0.5 mL; gray chromatograms) or after the pre-concentration (3.0 mL; black chromatograms), where an increase in the TAZ and PAZ responses is seen for both TIC and EIC chromatograms. Besides the six-fold increase in fungicide responses, the response of wood leachate components increased comparatively less and did not interfere with the fungicide detection.

The quantified TAZ and PAZ amounts in the industrial leachate are summarized in Table 3. The amounts of leached fungicides decreased each week with the TAZ concentration being slightly greater than that of PAZ, which is in agreement with the previously published results [42]. The intra-day repeatability of the LC-ESI-TOFMS analysis was investigated by analyzing the wood leachate from week 1 and 2 in triplicate. Good

repeatability was achieved for the two triazoles with the relative standard deviations (RSDs) $\leq 2\%$. Also, the inter-day repeatability was assessed by repeating the analysis after 4 days. The RSDs ranged between 1% and 7%, which was considered acceptable.

Table 3. Intra- and inter-day repeatability of triazole determination in industrial wood leachate samples.

	TAZ [$\mu\text{g}\cdot\text{L}^{-1}$]		PAZ [$\mu\text{g}\cdot\text{L}^{-1}$]	
	mean	% RSD	mean	% RSD
Inter-day Repeatability (4 days)				
Week 1 leachate	342	5	251	5
Week 2 leachate	213	5	166	1
Week 3 leachate	134	4	108	4
Week 4 leachate	72	4	62	7
Intra-day Repeatability (n = 3)				
Week 1 leachate	356	1	263	1
Week 2 leachate	220	2	172	1

4. Conclusions

An optimized LC-ESI-TOFMS method for triazole and IPBC quantification in wood leachate was developed while employing SPE-HLB sample pre-concentration, showing 91-102% analyte recoveries. The optimal LC-ESI conditions included an ACN-water solvent system with ammonium acetate as an electrolyte. Using a DOE response surface design, the optimal electrolyte concentration was found to be 1.7 mM, with a capillary voltage of 4350 V and a fragmentor voltage of 115 V. The matrix-affected LODs varied between 0.4–0.5 $\mu\text{g}\cdot\text{L}^{-1}$, and the matrix-affected LOQs were 1.2–1.5 $\mu\text{g}\cdot\text{L}^{-1}$. The developed method was successfully applied to the analysis of industrial wood leachates.

The intra-day repeatability was $\leq 2\%$, and the inter-day repeatability varied between 1–7%.

Acknowledgements

Marvin Windows and Doors is acknowledged for financial support. The authors would like to thank Ben Wallace for stimulating discussions and the provided industrial wood leachate samples. The authors are also grateful to Evguenii I. Kozliak for manuscript editing.

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