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Optimization of Pirimicarb and Its Metabolites by Ultra-Performance Liquid Chromatography-Tandem Mass Spectrometry

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Abstract - Pesticides enhance crop productivity but leave residues that threaten the health and the environment, necessitating sensitive analytical methods to detect widely used compounds like pirimicarb. This study focuses on optimizing the analysis of pirimicarb and its metabolites using liquid chromatography-tandem mass spectrometry (LC-MS/MS). Key instrumental parameters including interface temperature, desolvation line temperature, heat block temperature, column oven temperature, collision-induced dissociation (CID) gas pressure, and interface voltage were systematically optimized to enhance method sensitivity and reliability. Among the tested conditions, interface temperatures of 150 °C and 400 °C provided the highest signal intensity for pirimicarb, while pirimicarb-desmethyl responded best at 250 °C, and pirimicarb-desmethyl-formamido showed maximum signals at 150 °C and 300 °C. For desolvation line temperature, 150 °C yielded the highest intensities for pirimicarb and pirimicarb-desmethyl, whereas 200 °C was optimal for pirimicarb-desmethyl-formamido. Pirimicarb exhibited peak response at a heat block temperature of 300 °C, while pirimicarb-desmethyl showed comparable intensities at 100, 200, and 350 °C, and pirimicarb-desmethyl-formamido responded best at 100 and 200 °C. Column oven temperatures of 40 °C and 50 °C enhanced the response for pirimicarb, with pirimicarb-desmethyl and pirimicarb-desmethyl-formamido showing optimal intensities at 50 °C. Additionally, a CID gas pressure of 270 kPa and interface voltage of 4.0 kV produced the highest ionization efficiency across all analytes. The results demonstrated that specific parameter adjustments significantly improved ionization efficiency and signal intensity, leading to a more robust analytical method. This study underscores the importance of systematic parameter optimization in LC-MS/MS for accurate pesticide residue detection and provides a framework for future research on other pesticide groups.

Keywords *– Food safety, LC–MS/MS, method validation, pesticide residue, electrospray ionization*

1. Introduction

Pesticides are synthetic chemicals used in agricultural production to combat pests and plant pathogens. These substances aim to increase agricultural productivity by preventing crop losses caused by harmful organisms. The rapid efficacy and ease of use of pesticides have made them one of the most preferred agricultural inputs. However, the intensive and uncontrolled use of pesticides poses serious risks to the environment and human health [1, 2]. The contamination caused by pesticide residues in food products can lead to acute and chronic poisoning, negatively affecting the immune, nervous, and hormonal systems. Some types of pesticides have carcinogenic, mutagenic, and teratogenic effects, which are more severely felt by children and vulnerable groups [3-6].

Environmentally, pesticides have the potential to be transported through soil, water, and air, spreading over wide areas. This situation can lead to reduced biodiversity and severe disruption of the natural ecosystem

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balance. Pesticides contaminating water sources reduce drinking water quality and cause toxic effects on aquatic organisms. These toxic chemicals accumulating in soil negatively affect microbial activities and soil fertility, threatening sustainable agriculture [3, 4]. Chemically, pesticides are classified into two main groups: organic and inorganic compounds. Organic compounds constitute the majority of pesticides. Today, commercially used pesticides are classified based on their chemical structures and functional groups as organochlorine, organophosphorus, synthetic pyrethroid, and carbamate pesticides [1]. Carbamate pesticides are increasingly used in pest control due to their broad-spectrum biological activities and lower environmental persistence than organochlorine and organophosphorus pesticides [7-9]. However, despite their advantages, the increased application of synthetic pyrethroids and organophosphorus pesticides poses significant chronic and acute toxicity risks to aquatic organisms, including invertebrates, mollusks, and fish [10]. Carbamate pesticides consists of carbamic acid esters called N-methylcarbamates. However, the misuse and overuse of carbamate pesticides can lead to toxic effects on aquatic organisms and soil microorganisms, causing environmental imbalance. Particularly, pirimicarb attracts attention due to its potential risks to human health, necessitating precise analysis of such substances.

The analysis of carbamate pesticide residues is considered a high sensitivity but complex process. Various analytical methods have been developed to detect these residues in recent years. Gas chromatography (GC) and liquid chromatography (LC) are among the chromatographic techniques frequently used in these analyses. However, thermal stability issues during the analysis of N-methylcarbamate compounds using gas chromatography have made liquid chromatography a more suitable method for such analyses [7, 11, 12]. Liquid chromatography-tandem mass spectrometry (LC-MS/MS) plays a critical role in the sensitive and selective detection of pesticide residues and degradation products [13].

International authorities continuously update the maximum residue limits (MRLs) for pesticide residues in food to ensure public health and environmental sustainability [14]. For instance, the MRL value of oxamyl, a carbamate pesticide, was reduced 100-fold in 2024 for many products, lowering it to 0.001 mg/kg [15]. This situation suggests that similar restrictions may be imposed on other active substances. Detecting pesticide residues at low MRL values is crucial for protecting public health and developing reliable analytical methods.

In this study, the optimization of various parameters, such as interface temperature, desolvation line temperature, heat block temperature, column oven temperature, collision-induced dissociation (CID) gas, and interface voltage, was carried out to enhance the sensitivity and reliability of LC-MS/MS analysis for pirimicarb and its metabolites.

The following sections of this paper are arranged as follows: Section 2 describes the materials, chemicals, and instrumentation used, along with the experimental design and analytical methods. Section 3 presents the results and discussion, focusing on the impact of optimized LC-MS/MS parameters on the sensitivity and reliability of pirimicarb residue analysis. Finally, Section 4 concludes the study, summarizing key findings and suggesting future research directions.

2. Materials and Methods

2.1. Reference Materials and Chemicals

The pesticide reference materials of pirimicarb, pirimicarb-desmethyl, and pirimicarb-desmethyl-formamido (with 99.17%, 99.30%, and 98.52% purity, respectively) were procured from LGC. Methanol and ammonium formate with purity over 99.0% were supplied by Millipore.

2.2. Instrumentation

The analyses used a Shimadzu® LC-MS 8050 system, renowned for its advanced UPLC and MS/MS capabilities. Chromatographic separation was executed on a Raptor Biphenyl (2.1 mm x 100 mm, 2.7 µm particle size) from Restek Pure Chromatography (USA). The mobile phase comprised 10 mmol L^{-1} ammonium formate in distilled water (A) and methanol (B). The mobile phase gradient initiated at 45% B, ramped up to 95% B over 5.5 minutes, returned to 45% B at 5.51 minutes, and was maintained at 50% B from 5.51 to 7 minutes. Each sample injection volume was precisely 5 µL. The mobile phase flow rate was consistently maintained at 0.4 mL min^{-1}. LabSolution® software (version 5.118) was used to manage all instrument parameters precisely.

The chromatographic separation and retention times of pirimicarb and its metabolites (pirimicarb-desmethyl and pirimicarb-desmethyl-formamido) are illustrated in Figure 1. The chromatogram was obtained under the following optimized LC-MS/MS conditions: interface temperature of 150 °C, desolvation line temperature of 150 °C, heat block temperature of 300 °C, column oven temperature of 50 °C, collision-induced dissociation (CID) gas pressure of 270 kPa, and interface voltage of 4.0 kV.

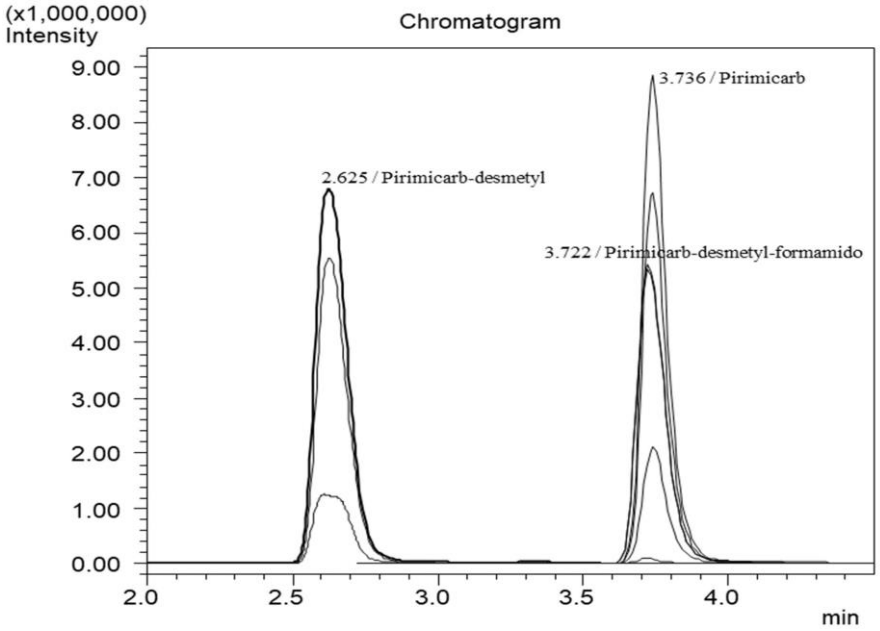

Figure 1. Chromatograms of pirimicarb, pirimicarb-desmethyl, and pirimicarb-desmethyl-formamido

2.3. Design of Experiments

The experimental run sequence of pirimicarb, pirimicarb-desmethyl, and pirimicarb-desmethyl-formamido performed on the LC-MS/MS system was presented in Table 1. Each injection was replicated three times.

Table 1. Experimental design for optimization parameters

Run	Interface temp. (°C)	Desolvation line temp. (°C)	Heat Block temp. (°C)	Column oven temp. (°C)	CID gas (kPa)	Interface voltage (kV)
1	100	250	400	40	270	4.0
2	150	250	400	40	270	4.0
3	200	250	400	40	270	4.0
4	250	250	400	40	270	4.0
5	300	250	400	40	270	4.0
6	350	250	400	40	270	4.0
7	400	250	400	40	270	4.0
8	150	100	400	40	270	4.0
9	150	150	400	40	270	4.0
10	150	200	400	40	270	4.0

Table 1. (Continued) Experimental design for optimization parameters

Run	Interface temp. (°C)	Desolvation line temp. (°C)	Heat Block temp. (°C)	Column oven temp. (°C)	CID gas (kPa)	Interface voltage (kV)
11	150	300	400	40	270	4.0
12	300	300	400	40	270	4.0
13	150	150	100	40	270	4.0
14	150	150	150	40	270	4.0
15	150	150	200	40	270	4.0
16	150	150	250	40	270	4.0
17	150	150	300	40	270	4.0
18	150	150	350	40	270	4.0
19	150	150	400	40	270	4.0
20	150	150	300	20	270	4.0
21	150	150	300	30	270	4.0
22	150	150	300	40	270	4.0
23	150	150	300	50	270	4.0
24	150	150	300	50	200	4.0
25	150	150	300	50	230	4.0
26	150	150	300	50	270	0.0
27	150	150	300	50	270	1.0
28	150	150	300	50	270	1.5
29	150	150	300	50	270	2.0
30	150	150	300	50	270	2.5
31	150	150	300	50	270	3.0
32	150	150	300	50	270	3.5

3. Results and Discussion

3.1. The Precursor Ions, Product Ions and Collision Energy of Pirimicarb and Its Metabolites

In this study, structures and the mass spectrums of pirimicarb and its metabolites (pirimicarb-desmethyl and pirimicarb-desmethyl-formamido) were analyzed (Figure 1-3). The reference materials were directly injected into the LC–MS/MS system at 1000 µg kg^{-1} concentration. In the pirimicarb and metabolites mass spectrum, characteristic ion fragmentation patterns were identified. MS was initially run in full scan mode to identify precursor ions. Then, two product ions with the highest intensity of each precursor were selected, and their Q1-Q3 Pre-Bias and collision energies were determined (Table 2).

Table 2. MS parameters for the analysis of pirimicarb and metabolites

Analyte	Precursor Ion (m/z)	Product Ion (m/z)	Dwell Time (msec)	Q1 Pre Bias (V)	Collision energy (eV)	Q3 Pre Bias (V)
Pirimicarb	239.3	72.2	100.0	-11.0	-22.0	-13.0
		182.3	100.0	-12.0	-15.0	-19.0
Pirimicarb-desmethyl	225.3	72.2	100.0	-21.0	-23.0	-29.0
		168.3	100.0	-27.0	-15.0	-29.0
Pirimicarb-desmethyl-formamido	253.3	72.2	100.0	-20.0	-22.0	-30.0
		225.1	100.0	-20.0	-10.0	-14.0

3.2.1 Pirimicarb

The primary precursor ion for pirimicarb was observed at 239.3 m/z, corresponding to the protonated molecular ion $[M+H]^+$. The mass spectrum exhibited a precursor ion at 239.3 m/z, with major product ions detected at 72.2 and 182.3 m/z, as illustrated in Figure 2, which depicts the fragmentation pattern of pirimicarb.

m/z 72.2 ($C_4H_{10}N^+$): This ion results from the cleavage of the carbamate moiety, forming a stable fragment. m/z 182.3 ($C_{10}H_{10}N_3O_2^+$): This fragment is generated through the loss of the N-methylcarbamate group, stabilizing the remaining molecular structure.

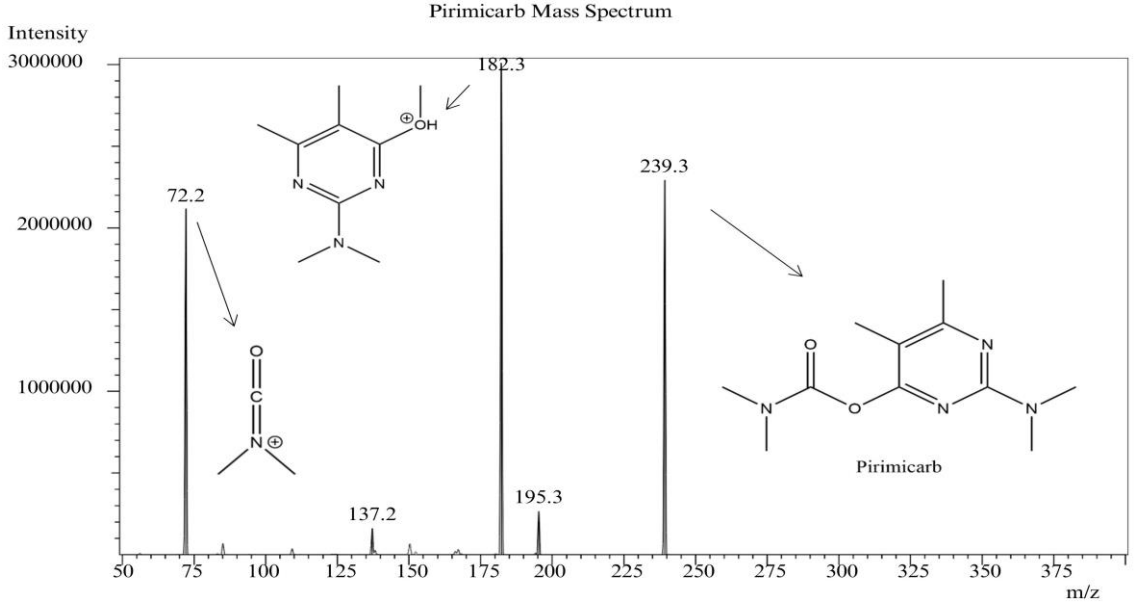

Figure 2. (+) ESI Mass spectrum of pirimicarb

3.2.2 Pirimicarb-Desmethyl

The primary precursor ion for pirimicarb-desmethyl was observed at 225.3 m/z, indicating the loss of a methyl (-CH_3) group from pirimicarb, forming the protonated molecular ion $[M+H]^+$. The precursor ion at 225.1 m/z generated characteristic product ions at 72.2 and 168.3 m/z, as shown in Figure 3, highlighting the pirimicarb desmethylation pathway.

m/z 72.2 ($C_4H_{10}N^+$): This ion results from the cleavage of the carbamate moiety, similar to pirimicarb. m/z 168.3 ($C_9H_{10}N_3O^+$): This fragment results from the loss of a methyl group (-CH_3), confirming the desmethylation process (Figure 3).

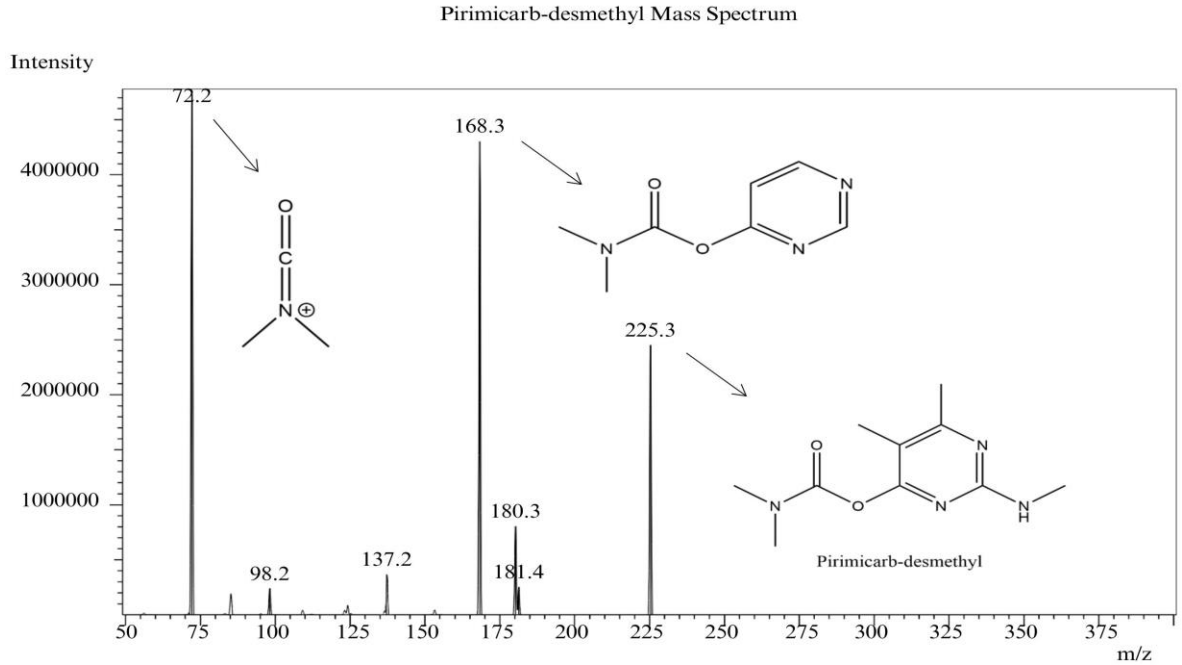

Figure 3. (+) ESI Mass spectrum of pirimicarb-desmethyl

3.2.3 Pirimicarb-Desmethyl-Formamido

The primary precursor ion for pirimicarb-desmethyl-formamido was observed at 253.3 m/z, which corresponds to the protonated molecular ion $[M+H]^+$, confirming the presence of an additional formamido (-NHCHO) functional group. The precursor ion at 253.3 m/z produced major fragments at 72.2 and 225.1 m/z, as demonstrated in Figure 4, confirming the formamido transformation process.

m/z 72.2 ($C_4H_{10}N^+$): Similar to the other metabolite, the loss of the carbamate moiety forms this ion. m/z 225.1 ($C_{11}H_{13}N_4O_2^+$): This fragment results from the loss of a formamido (-NHCHO) group, supporting the metabolite transformation process (Figure 4).

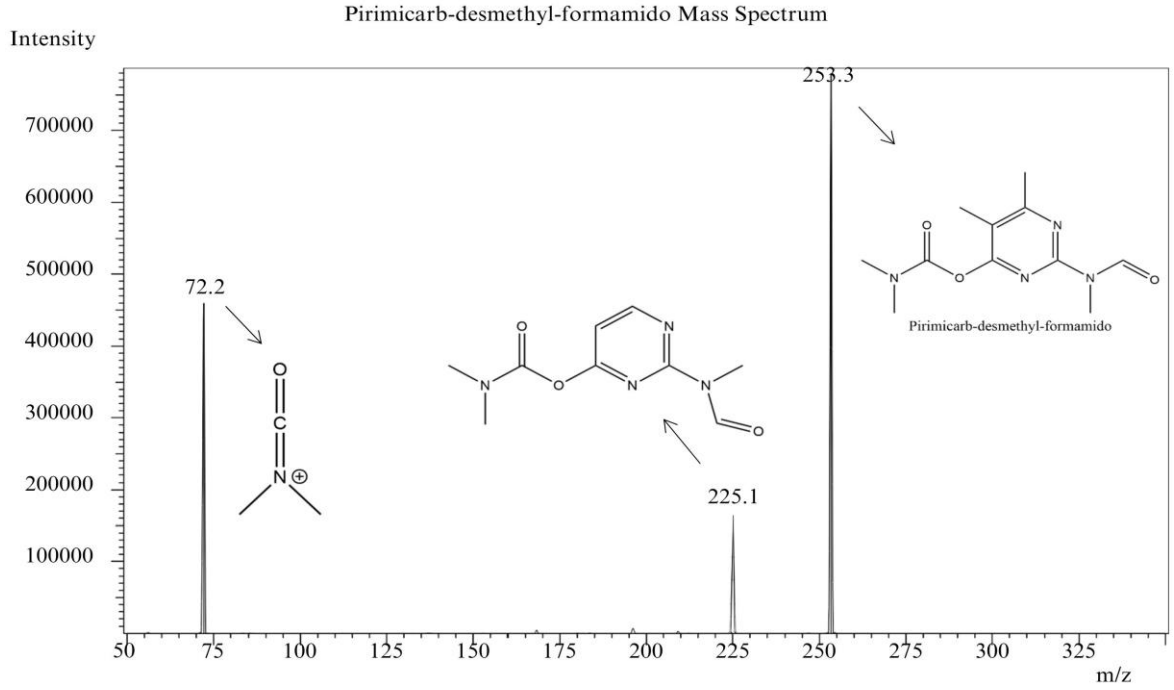

Figure 4. (+) ESI Mass spectrum of pirimicarb-desmethyl-formamido

The fragmentation pathways of pirimicarb and its metabolites were systematically analyzed, providing valuable insights into their structural stability and transformation mechanisms. The observed precursor and product ions confirmed the characteristic fragmentation patterns, supporting the reliability of LC-MS/MS in pesticide residue analysis. These findings contribute to optimizating of analytical methods for carbamate pesticides, ensuring enhanced sensitivity and selectivity in residue monitoring and regulatory compliance.

3.2. Optimization of Instrument Parameters For Pirimicarb and Its Metabolites

Liquid chromatography– tandem mass spectrometry is widely used for pesticide residue analysis due to its high sensitivity and selectivity. However, many LC–MS/MS parameters are typically set during method development and rarely revisited, potentially leading to suboptimal performance. Factors such as interface temperature, desolvation line temperature, heat block temperature, column oven temperature, CID gas, and interface voltage can significantly impact ionization efficiency and signal intensity. Optimizing these parameters ensures enhanced sensitivity, reproducibility, and method robustness.

In this study, instrument parameters were examined. The intensity values of pirimicarb, pirimicarb-desmethyl, and pirimicarb-desmethyl-formamido based on the device parameters interface temperature, desolvation line temperature, heat block temperature, column oven temperature, CID gas, and interface voltage are shown in Figures 5a, 5b, 5c, 5d, 5e, and 5f, respectively, listed in Table 2.

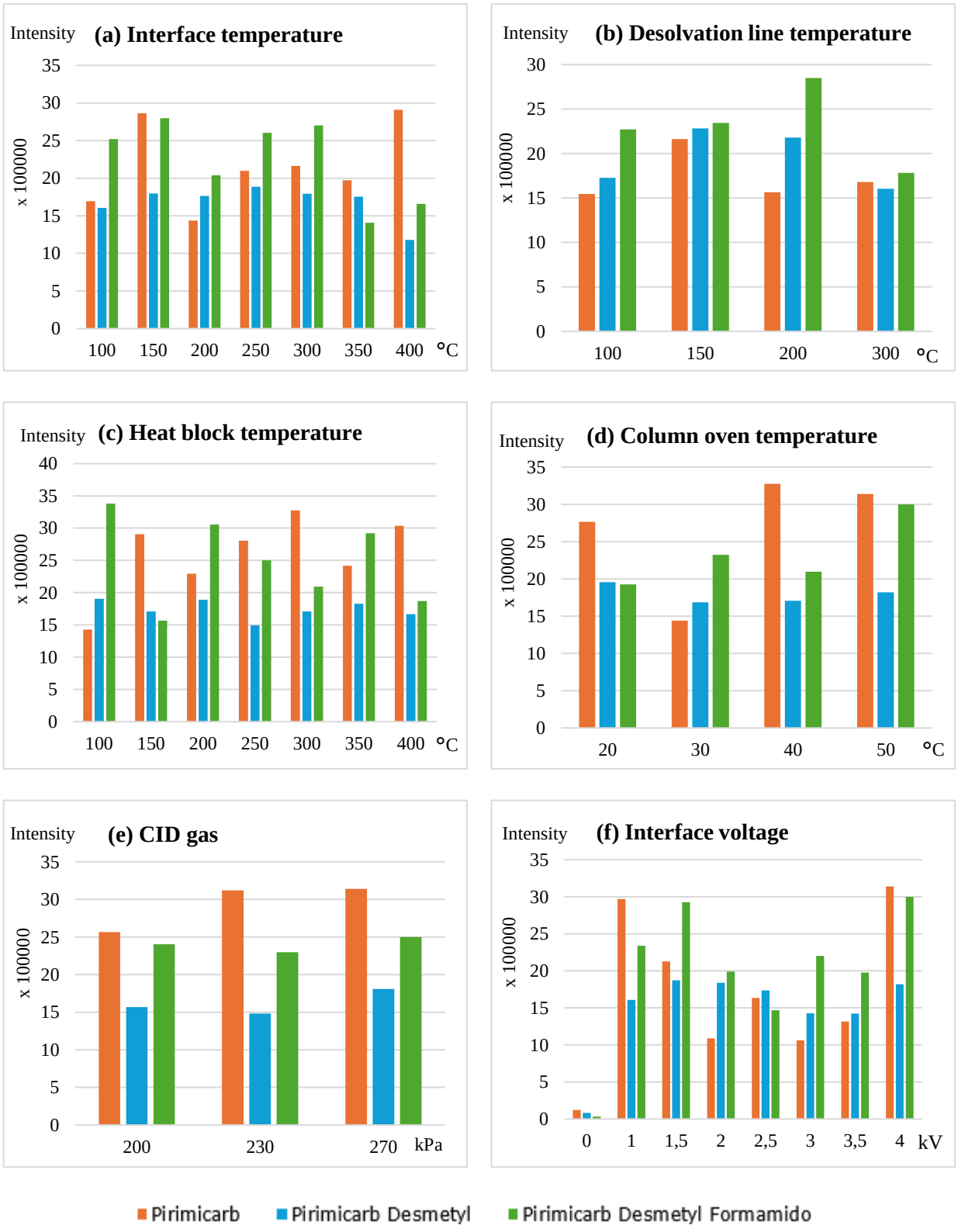

Figure 5. Effects of optimization parameters on signal intensity

3.2.1. Interface Temperature

The effect of interface temperature on signal intensity was assessed across seven temperature levels ranging from 100 to 400 °C. For pirimicarb, the highest intensities were recorded at both 150 and 400 °C, indicating a bimodal distribution. In contrast, pirimicarb-desmethyl exhibited its peak intensity at 250 °C. Pirimicarb-desmethyl-formamido demonstrated maximum responses at both 150 and 300 °C (Figure 5a). These results

show that the ideal interface temperature can vary depending on the compound. This highlights the importance of adjusting parameters specifically for each analyte to achieve better sensitivity and more reliable results.

3.2.2. Desolvation Line Temperature

The influence of desolvation line temperature on signal intensity was systematically evaluated at four temperature settings ranging from 100 to 300 °C. The results indicated that a temperature of 150 °C yielded the highest intensity values for pirimicarb and pirimicarb-desmethyl. However, pirimicarb-desmethyl-formamido demonstrated its maximum response at 200 °C (Figure 5b). These results show that each compound responds differently to temperature changes. It's important to adjust the analysis conditions based on the specific behavior of each analyte to get the most accurate and sensitive results.

3.2.3. Heat Block Temperature

For pirimicarb, the highest intensity was observed at 300 °C. Pirimicarb-desmethyl showed similar intensity values at 100, 200, and 350 °C, with no distinct optimum. Pirimicarb-desmethyl-formamido exhibited high intensity values at both 100 and 200 °C (Figure 5c). These observations highlight the importance of compound-specific optimization to ensure accurate and reliable results.

3.2.4. Column Oven Temperature

The column oven temperature was optimized using measurements at four different levels. Pirimicarb showed the highest intensity at 40 °C, with a very similar value also observed at 50 °C, whereas pirimicarb-desmethyl and pirimicarb-desmethyl-formamido exhibited their maximum signals at 50 °C (Figure 5d). These results show that the best column oven temperature can vary depending on the compound. This highlights how important it is to fine-tune the settings for each analyte to get consistent and dependable results.

3.2.5. Collision-Induced Dissociation (CID Gas)

The CID gas analysis showed that the default value of 270 kPa produced the highest intensity for pirimicarb and its metabolites, suggesting that this parameter optimizes analytical performance (Figure 5e).

3.2.6. Interface Voltage

The Interface voltage of 4 kV provided the highest ionization efficiency for all analytes, making it the most suitable voltage for optimizing analytical performance (Figure 5f).

3.2.7. General Assessment

Previous studies have shown that LC-MS/MS instrument parameters are generally similar. These parameters have been widely applied in both multiple pesticide residue analysis [16-19] and single pesticide analysis [20-22]. However, further optimization tailored to the specific chemical properties of each analyte may be especially crucial for pesticides with very low MRL limits. While these parameters are often used in their default settings, some studies have shown that modifying them can improve analytical performance [23]. This highlights the importance of adjusting device settings in specific cases to better meet the requirements of complex analyses.

The results show that optimizing the parameters of the LC-MS/MS method enhances analytical sensitivity and improves overall reliability. The desolvation temperature optimization studies conducted for metformin and rosiglitazone align with our findings, further supporting the applicability of the methodology [24]. Likewise,

studies on CTX1B and CTX3C ciguatoxins demonstrated that optimizing gas and sheath gas temperatures significantly improved analytical performance [25]. The importance of optimizing column oven temperature has been highlighted in the literature as a key factor for achieving accurate and reliable results in complex matrices [26]. Our findings confirm that optimizing column oven temperature increased the intensity of pirimicarb and its metabolites.

These results emphasize the importance of parameter optimization in LC-MS/MS methods, especially for pesticide residue analysis. Previous studies have shown that variations in DL temperature and column oven temperature can significantly affect signal intensity and detection limits, depending on the chemical structure of the analyte [24,26]. Our findings are consistent with such observations, particularly the compound-specific responses observed at different column and desolvation line temperatures. These comparisons highlight the practical relevance of tailored optimization and support its contribution to more accurate residue quantification. Future research should investigate similar optimization strategies for other pesticide groups.

4. Conclusion

This study demonstrated that systematic optimization of instrumental parameters in ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS) significantly improves the detection of pirimicarb and its metabolites (pirimicarb-desmethyl and pirimicarb-desmethyl-formamido). Key parameters—including interface temperature, desolvation line temperature, heat block temperature, column oven temperature, CID gas pressure, and interface voltage—were individually evaluated. The optimized settings enhanced ionization efficiency, signal intensity, reproducibility, and overall method robustness. Compared to default settings, the optimized conditions enhanced reproducibility and detection limits, making the method more robust and suitable for regulatory pesticide residue monitoring. These findings underscore the necessity of systematic parameter adjustments in LC-MS/MS methodologies to achieve accurate and reliable pesticide quantification. Additionally, the optimization strategies established in this work are expected to benefit pesticide residue analyses that require high sensitivity. The findings contribute to the development of high-performance and sustainable analytical methods that support food safety and meet stringent regulatory standards. Future research should explore similar optimization strategies for other pesticide groups, assess matrix effects, and integrate advanced sample preparation techniques to further improve sensitivity and selectivity in pesticide residue analysis.

Author Contributions

They all read and approved the final version of the paper.

Conflict of Interest

All the authors declare no conflict of interest.

Ethical Review and Approval

No approval from the Board of Ethics is required.

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