Optimization and Selection of Mobile Phase for the Determination of Multiple Pesticide Standards Using Liquid Chromatography-Tandem Mass Spectrometry

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Abstract: The selection of the best mobile phase setup is one of the most important factors to be considered prior to quantitative instrumentation of multiple pesticides. Usually, mobile phases comprises of water (A) and an organic solvent (B) are the setup used in liquid chromatography instruments for the analysis of pesticide residues in various samples. Unfortunately, most of the analyses are being carried out without optimization and selection of the best mobile phase setup to improve the sensitivity of the instrument. For that reason, the comparative analysis of the reportedly used mobile phases and some few suggested ones was carried out on the multi-pesticide mixture of 0.1 mg/kg (100 µg/kg) standard solutions and quantified with liquid chromatography-tandem mass spectrometry (LC-MS/MS) instrument. Consequently, the best mobile phases setup that resulted in the sum of average total chromatographic peak areas (ATCPAs) and average total chromatographic peak heights (ATCPH) for the total ion chromatography (TIC) scans as an index that correspond to the concentration levels was selected [0.1% formic acid in H_2O (A) and 0.1% formic acid in acetonitrile (ACN) (B)]. And further optimization was successfully carried out on the selected mobile phase-A and the resulted setup [1% ACN and 0.1% formic acid in Milli-Q-water (mobile phase A) coupled with 0.1% formic acid in ACN (mobile phase-B)] improved the instrumental sensitivity on the targeted analytes. Thus, this justify the potential benefits of optimizing setup of the mobile phases prior to LC-MS/MS instrumentation of multi-pesticide analytes.

Keywords: Mobile phase, Analysis of multi-pesticide residues, Liquid chromatography-tandem mass spectrometry, Total ion chromatography, Total chromatographic peak areas.

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INTRODUCTION

Foods are contaminated through various activities performed by man such as the accidental or intentional discharge of chemicals or waste substances from domestic, industrial and agricultural sites into the environment (1, 2). However, most of these contaminants are non-biodegradable, which can be easily transferred from the ground surface to the underground water because of their ability in dissolving sparingly in water (3, 4). At the long run, the contaminants pollute the foods through their respective circulatory movements in the environment (5). The contaminants include inorganic matters such as heavy metals (6-8), as well as organic chemicals such as heat-generated compounds [polycyclic aromatic hydrocarbons (PAHs) and acrylamide)] (9), organic polymers (bromodiphenyl ethers, chlorobiphenyls, chlorodibenzodioxins, chlorodibenzofurans, etc), mycotoxins (aflatoxins), perfluoroalkyl acids (10-12). Other contaminants with emerge-concerns include phthalates, bisphenol A, alkylphenols (13), phytosterols, estrogens, phytoestrogens (14), pharmaceuticals/veterinary drugs, synthetic dyes and pesticides (15-18).

Advantageously, pesticides have been used in domestic and agricultural practices for decades increasing the gross domestic products (GDP) of

many countries around the globe. But their dangers in handling and excessive usage have been the issues of concern due to their residual accumulations in food chain resulting in many health problems that include cancers, etc. However, there are challenges experienced in the determination of multiple residue of pesticide analytes in food samples. These could be due to extensive ranges of their chemical properties such as neutral, acidic and basic (19), vapor pressure/Henry's law constant (20), solubility (21), partition coefficient in octanol/water (log*P*) (22) and acid dissociation constant (pK_a) (23). Besides, the analytical samples also play challenging roles for pesticides extraction during sample preparation because of their features that include non-polar, polar, fatty and waxy samples (24, 25).

Even though the conventional methods such as liquid-liquid extraction (LLE), liquid-phase microextraction (LPME) as well as solid phase extraction (SPE) techniques were previously used as the sample preparation methods for the multiple pesticides analysis (16), they possess poor efficiency and selectivity of the targeted, which were their major drawbacks (26). Also, many detectors and quantification instruments were used previously for the analyses of multiple pesticide residues (26). These instruments include the gas chromatography-atomic emission detector (GC-AED) (27) and the high performance liquid chromatography (HPLC) (28). Other instruments include gas chromatography-tandem mass spectrometry (GC-MS/MS) (29) and liquid chromatography-tandem mass spectrometry (LC-MS/MS) (30). Unfortunately, the poor sensitivity of these instruments is their major setbacks. Fortunately, the shortcomings of the conventional sample preparation techniques and that of the detecting and quantifying instruments could be corrected through optimization such as the use of response surface methodology (RSM) (26, 31).

Accordingly, these compel food safety analysts to improve better ways of analyzing multi-pesticide residues in food samples through effective sample preparations and instrumentation techniques. For instance, RSM optimization of the instrumental parameters for LC-MS/MS (advanced) instrument such as the setup of the mobile phases could provide better results of pesticides determination at the lower concentration levels.

Usually, mobile phases comprise of Milli-Q-water (A) and an organic solvent (B) setup are used in the liquid chromatography instruments for the analyses of pesticide residues in various samples of food materials (26, 32, 33). In fact, the organic solvents such as acetonitrile (ACN) and methanol are significantly used in the reverse-phase of liquid chromatography (LC) due to their excellent compatibility (34).

Thus, the aim of this research is to comparatively study the most recently used (reported) setup of mobile phases and some few suggested ones (Table 2). The best mobile phases setup that provided highest average total chromatographic peak area (ATCPA) as an index that correspond to the concentration of analytes in the multi-pesticide mixture of standard solutions was selected after the LC-MS/MS instrumentation.

However, the multi-pesticides mixture of standard solutions of Dursban, Diazinon, Thiamethoxam, Metalaxyl, Thiobencarb, Baycarb, Carbaryl and Propamocarb (Figure 1) were analyzed for the purpose of the mobile phase optimization.

It is, therefore, hoped that the result of this study would serve as a reference guide for the future studies, and the optimized mobile phase setup would be routinely used in LC-MS/MS for the determination of multiple pesticide residues in various food samples.

Table 1: Auto-tuning and Mass-Hunter optimization results of the instrument using the multi-pesticides mixture of standard solutions

Pesticide	MF	MIM	TOP	COC	IM (ESI)	PI	MRM_1/MRM_2	CE_1/CE_2	ART
Dursban (Chlorpyrifos)	$C_9H_{11}Cl_3NO_3PS$	349	Insecticide & Nematicide	Organophosphorus	$[M+H]^+$	350	96.8/197.9	34/22	11.36
Diazinon	$C_{12}H_{21}N_2O_3PS$	304	Insecticide	Organophosphorus	$[M+H]^+$	305	96.9/169.1	42/22	10.22
Thiamethoxam	$C_8H_{10}ClN_5O_3S$	292	Insecticide	Neonicotinoid	$[M+H]^+$	292	132/211	26/10	2.68
Metalaxyl	$C_{15}H_{21}NO_4$	279	Fungicide	Xylylalanine	$[M+H]^+$	280	160.1/220.1	26/10	7.33
Thiobencarb	$C_{12}H_{16}ClNOS$	257	Herbicide	Thiocarbamate	$[M+H]^+$	258	89.1/125	54/26	10.34
Baycarb (Fenobucarb)	$C_{12}H_{17}NO_2$	207	Insecticide	Carbamate	$[M+H]^+$	208	77/95	42/10	8.34
Carbaryl	$C_{12}H_{11}NO_2$	201	Insecticide & Nematicide	N-Methyl Carbamate	$[M+H]^+$	202	127.1/145	30/6	7.16
Propamocarb	$C_9H_{20}N_2O_2$	188	Fungicide	Other Carbamate	$[M+H]^+$	189	74/102.1	26/14	1.36

PIN, pesticide identity number; MF, molecular formula; MIM, mono-isotopic mass; TOP, type of pesticide; COC, class of chemical; IM, ionization mode; ESI, electrospray ionization; PI, precursor ion (m/z); MRM, multiple reactions monitoring; CE, collision energy (eV); ART, average retention time (min)

Table 2: The list of suggested and reported mobile phases used for the optimization

	References	Water (A)	Organic Mobile Phase (B)
1.	1st suggested mobile phase	A	ACN
2.	Rajski, Lozano (35), Pérez-Ortega, Gilbert-López (54)	A + 0.1% FA	ACN
3.	, Economou, Botitsi (56) and Lucas (57)	A + 0.1% FA	ACN + 0.1% FA
4.	Vázquez, Lozano (36)	A + 0.1% FA	ACN + 0.1% FA + 5% A
5.	2nd suggested mobile phase	A	MeOH
6.	Golge and Kabak (58)	A + 5 mM AF	MeOH + 5 mM AF
7.	Zanella, Munaretto (43)	A + 2% MeOH + 0.1% FA + 5 mM AF	MeOH + 0.1% FA + 5 mM AF
8.	3rd suggested mobile phase	A	MeOH/ACN (1:1)
9.	4th suggested mobile phase	A + 5 mM AF + 0.1%FA	MeOH/ACN (1:1) + 0.1% FA + 5 mM AF

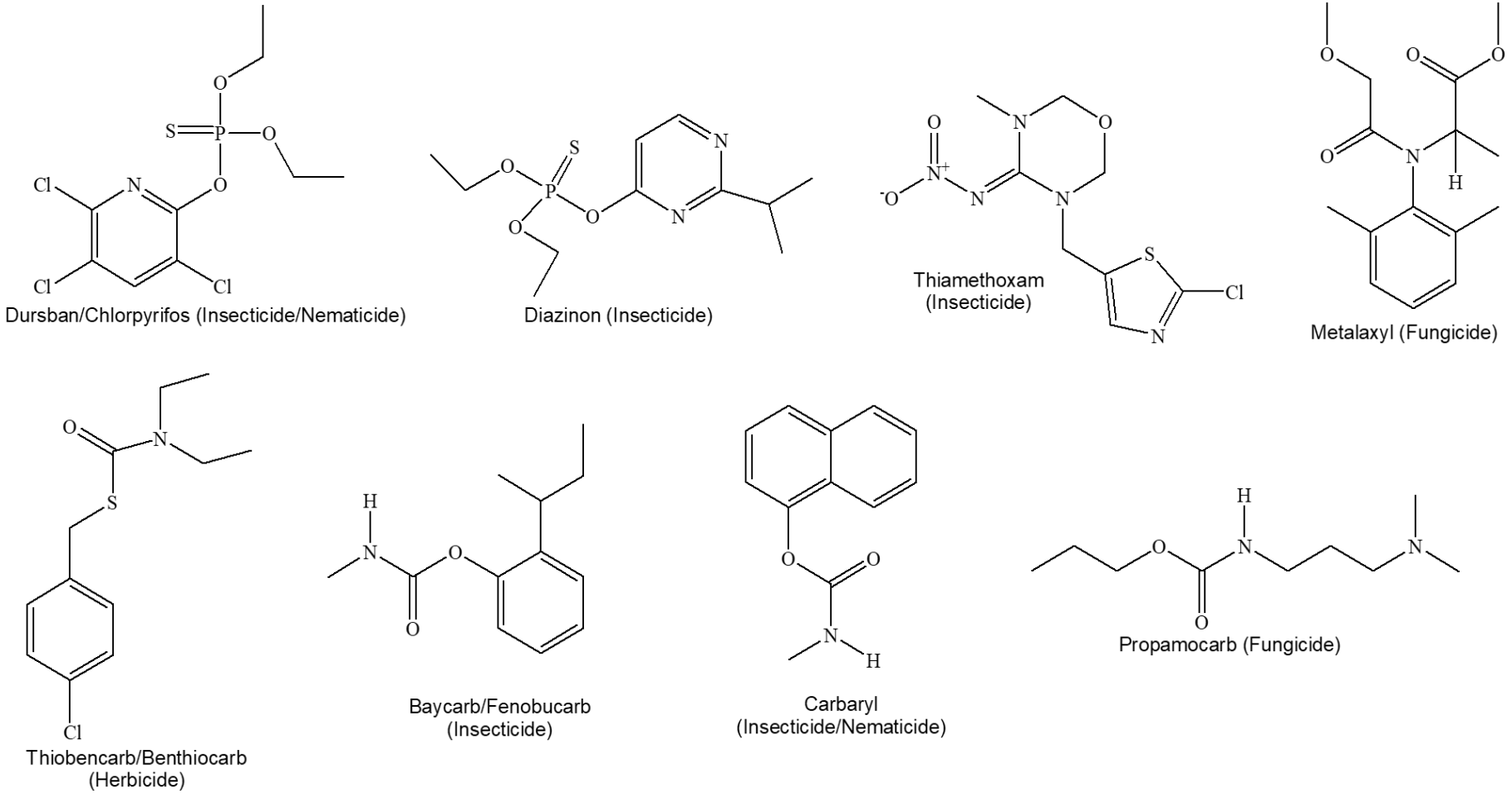

Figure 1: Structural formula of the analyzed pesticide residues

MATERIAL AND METHODS

The chemicals and reagents such as the stock standard solution (100 mg/kg) for pesticide Baycarb,

Carbaryl, Diazinon, Dursban, Metalaxyl, Propamocarb, Thiamethoxam and Thiobencarbwere were purchased from AccuStandard® (New Haven, USA). The LC-MS grade organic solvents that include ACN and methanol were purchased from Merck (Germany). The formic acid was purchased from Fisher Scientific. The Millipore-filtered (deionized) water was obtained using Merck Millipore water purification system (Billerica, USA). While, the apparatus and equipments that include the 100 and 500 µL microsyringe were purchased from Agilent (Australia). The pH meter PB was purchased from Sartorius group (Germany). The HPLC autosampler vials were purchased from Agilent Technologies (USA). The Supelco HPLC column [Ascentis® Express C_{18} (5 cm x 2.1 mm, 2.7 µm)] was purchased from Sigma-Aldrich (USA). And the liquid chromatography-tandem mass spectrometry (LC-MS/MS) [triple quadrupole (G6490A) built in Electrospray ESI (±) MS/MS Sensitivity and Jet stream Technology] instrument was purchased from Agilent (Singapore).

Conditioning of the LC-MS/MS

The following contributory parameters of the LC-MS/MS instrument were setup initially that include; analyte injection volume (5 µL), flow rate (0.1 mL/min), column temperature (30 ºC), gas temperature (200 ºC), nebulizer gas (45 psi), gas flow (14 L/min), sheath gas temperature (400 ºC), capillary voltage (3000 V), sheath gas flow (11 L/min), and delta$^{(+)}$ EMV (200 V). However, these factors contributed in determining optimum fragmentor voltage and the four-fragmentor product ions with their respective retention time (RT) and collision energy (CE) (Table 1). Moreover, the instrumental default settings were further used for the development of the best gradient program runs for the mobile phase-B elution time by adopting and modifying the methods used by Rajski, Lozano (35) and Vázquez, Lozano (36) for analysis of similar multi-pesticide compounds. This results in the best shortest elution time, which provided the best total ion chromatography (TIC) peaks resolution for the LC-MS/MS instrumentation (Figure 2). However, TIC resolution provided an optimum condition for the attainment of higher total chromatographic peak area (TCPA) (37) and mathematically expressed in Equation 1 (38).

Therefore,

$$TCPA = \sum CPA \qquad \text{(Eq. 1)}$$

Where
TCPA is the total chromatographic peak area and CPA is the chromatographic peak area.

Notably, the best setup of mobile phases were also selected using the initial settings of the instrument. Therefore, the TCPA obtained from LC-MS/MS analysis serves as an index used for estimating the number of target analytes that are present in the analyzed samples (31). It is because of the close similarities range of the resulted peak areas due to the log*P* of targeted analytes. Moreover, the peak areas maybe correlated and categorically suitable for multiple pesticides analysis using the LC-MS/MS instrument (39).

Sample Treatment and Methodology

The stock standard solution of 100 µg/mL that is equivalent to 100 mg/kg (i.e. 100,000 µg/kg) or parts per million (ppm) (40) for each pesticide was diluted to 10, 1 and 0.1 mg/kg (100 µg/kg) with appropriate volumes of methanol. The appropriate volumes were calculated using the dilution formula as expressed in Equation 2 (41), separately. Afterward, the prepared working standard solutions were preserved in a refrigerator at 4 ºC before carrying out the LC-MS/MS analysis.

$$C_1C_2 = V_1V_2 \qquad \text{(Eq. 2)}$$

Where
C_1: The concentration of the stock standard solution,
C_2: The concentration of the working standard solution
V_1: The volume of the stock standard solution
V_2: The volume of the working standard solution.

Meanwhile, the selection of the LC-MS/MS mobile phase was carried out by optimization technique using one factor or variable at a time (OFAT or OVAT) based on the documentation of Sherma (42). However, the multivariate optimization technique was not favorable for the selection because responses for each of the mobile phase is required individually without interaction to estimate the actual effect of the mobile phase setup. Moreover, the two setups of mobile (organic and aqueous) phases are involved with interactive percentage flow of organic/aqueous changes to create an optimum condition of analytes detection.

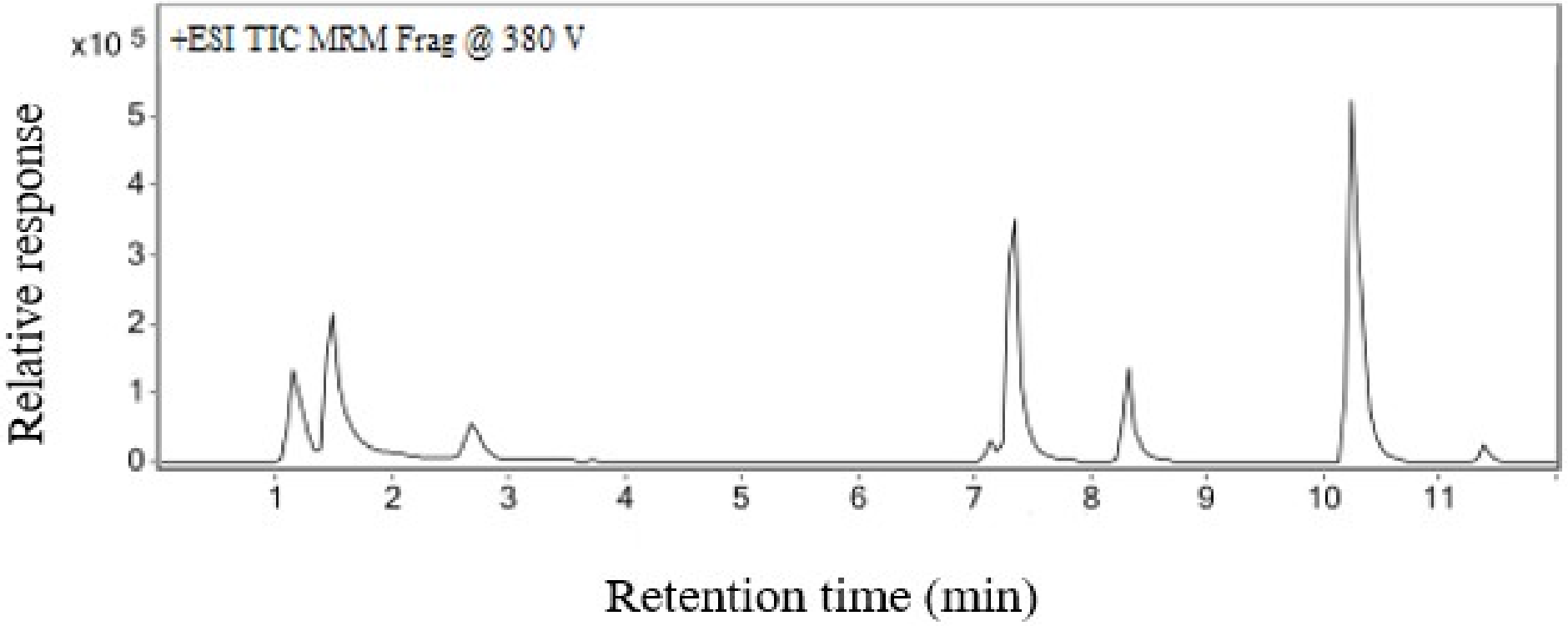

Figure 2: The total ion chromatography (TIC) of the analyzed pesticide standards.

Table 1: Auto-tuning and Mass-Hunter optimization results of the instrument using the multi-pesticides mixture of standard solutions

Pesticide	MF	MIM	TOP	COC	IM (ESI)	PI	MRM_1/MRM_2	CE_1/CE_2	ART
Dursban (Chlorpyrifos)	$C_9H_{11}Cl_3NO_3PS$	349	Insecticide & Nematicide	Organophosphorus	$[M+H]^+$	350	96.8/197.9	34/22	11.36
Diazinon	$C_{12}H_{21}N_2O_3PS$	304	Insecticide	Organophosphorus	$[M+H]^+$	305	96.9/169.1	42/22	10.22
Thiamethoxam	$C_8H_{10}ClN_5O_3S$	292	Insecticide	Neonicotinoid	$[M+H]^+$	292	132/211	26/10	2.68
Metalaxyl	$C_{15}H_{21}NO_4$	279	Fungicide	Xylylalanine	$[M+H]^+$	280	160.1/220.1	26/10	7.33
Thiobencarb	$C_{12}H_{16}ClNOS$	257	Herbicide	Thiocarbamate	$[M+H]^+$	258	89.1/125	54/26	10.34
Baycarb (Fenobucarb)	$C_{12}H_{17}NO_2$	207	Insecticide	Carbamate	$[M+H]^+$	208	77/95	42/10	8.34
Carbaryl	$C_{12}H_{11}NO_2$	201	Insecticide & Nematicide	N-Methyl Carbamate	$[M+H]^+$	202	127.1/145	30/6	7.16
Propamocarb	$C_9H_{20}N_2O_2$	188	Fungicide	Other Carbamate	$[M+H]^+$	189	74/102.1	26/14	1.36

PIN, pesticide identity number; MF, molecular formula; MIM, mono-isotopic mass; TOP, type of pesticide; COC, class of chemical; IM, ionization mode; ESI, electrospray ionization; PI, precursor ion (m/z); MRM, multiple reactions monitoring; CE, collision energy (eV); ART, average retention time (min)

Thus, comparative analysis was carried out on some assumed and selected mobile phases reportedly used for analysis of pesticides in various samples. Experimentally, the comparative analysis was carried out on the multi-pesticide mixture of 0.1 mg/kg multi-pesticide mixture of standard solutions. Consequently, the TIC of the instrumental runs for each of the mobile phases resulted in chromatographic peak heights (ATCPH), and areas (ATCPAs) as presented in Table 3. Then again, the addition of organic solvent into aqueous mobile phase could provide the optimum condition of log$P$, which contributes to the attainment of good condition for the multi-pesticide residues analysis in food samples using LC-MS/MS instrument as revealed (43). For this reason, optimization was carried out by serial addition of ACN into the aqueous mobile phase (0.1% FA milli-Q-water). Thus, the mobile phase setup that provided the best separation of analytes and the highest TCPA was selected for further optimization by adding 0, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 7.5 and 10% ACN in mobile phase A. Moreover, the best pH solution was selected based on the results of the average TCPA responses of the LC-MS/MS instrument.

RESULTS AND DISCUSSION

The responses of the screened mobile phases were compared and recorded. The mobile phase setup [0.1% formic acid in Milli-Q-water (A) and 0.1% formic acid in ACN (B)] was the best based on the highest results obtained [ATCPAs ± standard deviation (STDEV) as well as ATCPH± STDEV)] in triplicates as tabulated and illustrated in Table 3 and Figure 3, respectively. This result was also supported by other findings using the mobile phase for pesticides analysis (44, 45). Meanwhile, further optimization result of mobile phase-A after addition of ACN (0 - 10%) revealed that the addition of 1% ACN into 0.1% FA Milli-Q-water at an average pH of 3.50 ± 0.07 STDEV (mobile phase A) coupled with 0.1% FA in ACN at pH 6.56 ± 0.04 STDEV (mobile phase-B) provided the highest ATCPA (Table 4). The results were supported by their respective pH readings as shown in Table 4 and Figure 4, respectively. Moreover, the retention time (min) of the pesticide analytes were less than the results reported by some literatures such as thiamethoxam, 2.68 < 2.87 (46); propamocarb, 1.36 < 1.47 (47); carbaryl, 7.16 < 16.0 (48); metalaxyl, 7.33 < 17.90 (49); thiobencarb 10.34 < 10.76 (50), and dursban, 11.36 < 12.30 (51). But the retention time (min) of baycarb (8.34) and diazinon (10.22) were more than 6.73 (52) and 7.09 (53) respectively. Fortunately, the optimized mobile phase contributes towards shortening the total run time (min) for the multiple pesticides analysis using the LC-MS/MS instrument.

CONCLUSION

The selection and optimization of the best mobile phase setup was successfully carried out. Eventually, the optimized mobile phase setup [1% ACN and 0.1% FA in Milli-Q-water (mobile phase-A) coupled with 0.1% FA in ACN (mobile phase-B)] improved the instrumental sensitivity on the targeted analytes. Thus, this justify the potential benefits of optimizing setup of the mobile phases prior to LC-MS/MS instrumentation of multi-pesticide analytes. Also, the selected and optimized mobile phase setup could be used for the analysis of other contaminants with similar properties to the analyzed pesticide compounds.

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CONFLICT OF INTEREST

The authors of this research agreed with no conflicts of interest.

Table 3: The ATCPH and ATCPA Instrumental responses for the selection of mobile phase

Ref codes	References	Water (A)	Organic M/Phase (B)	% M/Phase B	ATCPH ± STDEV	ATCPA ± STDEV
A	1st suggested mobile phase	A	ACN	25	(361 ± 2) x10^5	(47 ± 3) x 10^7
B	Rajski, Lozano (35), Pérez-Ortega, Gilbert-López (54)	A + 0.1% FA	ACN	30	(349 ± 3) x 10^5	(46 ± 1) x 10^7
C	, Economou, Botitsi (56) and Lucas (57)	A + 0.1% FA	ACN + 0.1% FA	15	(50 ± 1) x 10^6	(72 ± 9) x 10^7
D	Vázquez, Lozano (36)	A + 0.1% FA	ACN + 0.1% FA + 5% A	30	(31 ± 2) x 10^6	(38 ± 1) x 10^7
E	2nd suggested mobile phase	A	MEOH	30	(17 ± 1) x 10^6	(23 ± 2) x 10^7
F	Golge and Kabak (58)	A + 5 mM AF	MEOH + 5 mM AF	30	(26 ± 2) x 10^6	(30 ± 1) x 10^7
G	Zanella, Munaretto (43)	A + 2% MEOH + 0.1% FA + 5 mM AF	MEOH + 0.1% FA + 5 mM AF	10	(58 ± 3) x 10^6	(60 ± 7) x 10^7
H	3rd suggested mobile phase	A	MEOH/ACN (1:1)	30	(27 ± 1) x 10^6	(30 ± 4) x 10^7
I	4th suggested mobile phase	A + 5 mM AF + 0.1%FA	MEOH/ACN (1:1) + 0.1% FA + 5 mM AF	25	(36 ± 5) x 10^6	(32 ± 3) x 10^7

ATCPH, average total chromatographic peak height; ATCPA, average total chromatographic peak area; RT, retention time; AF, ammonium formate; FA, formic acid; STDEV, standard deviation; Ref, reference

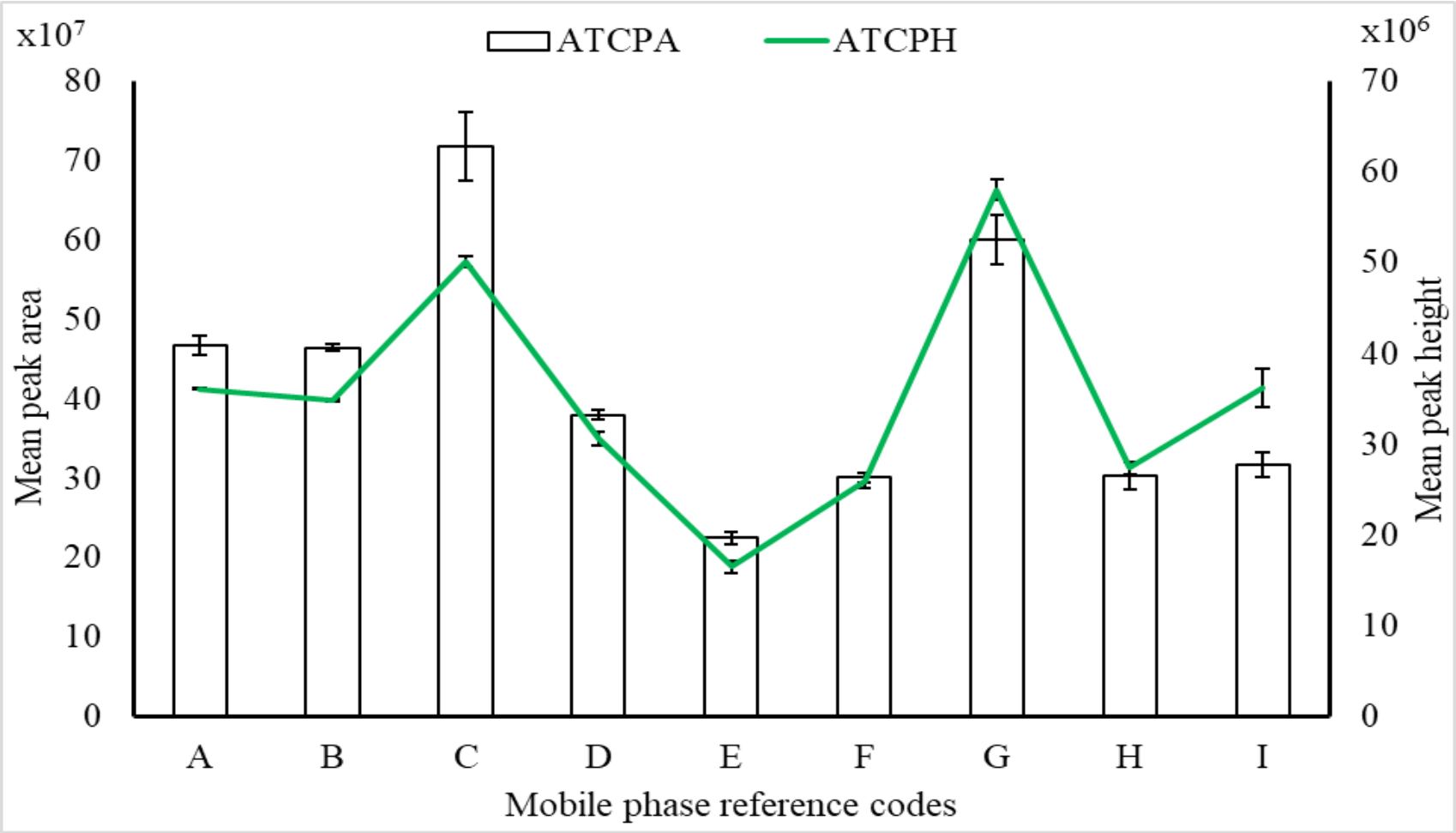

Figure 3: The comparative studies of ATCPA and ATCPH results for the analyzed mobile phases

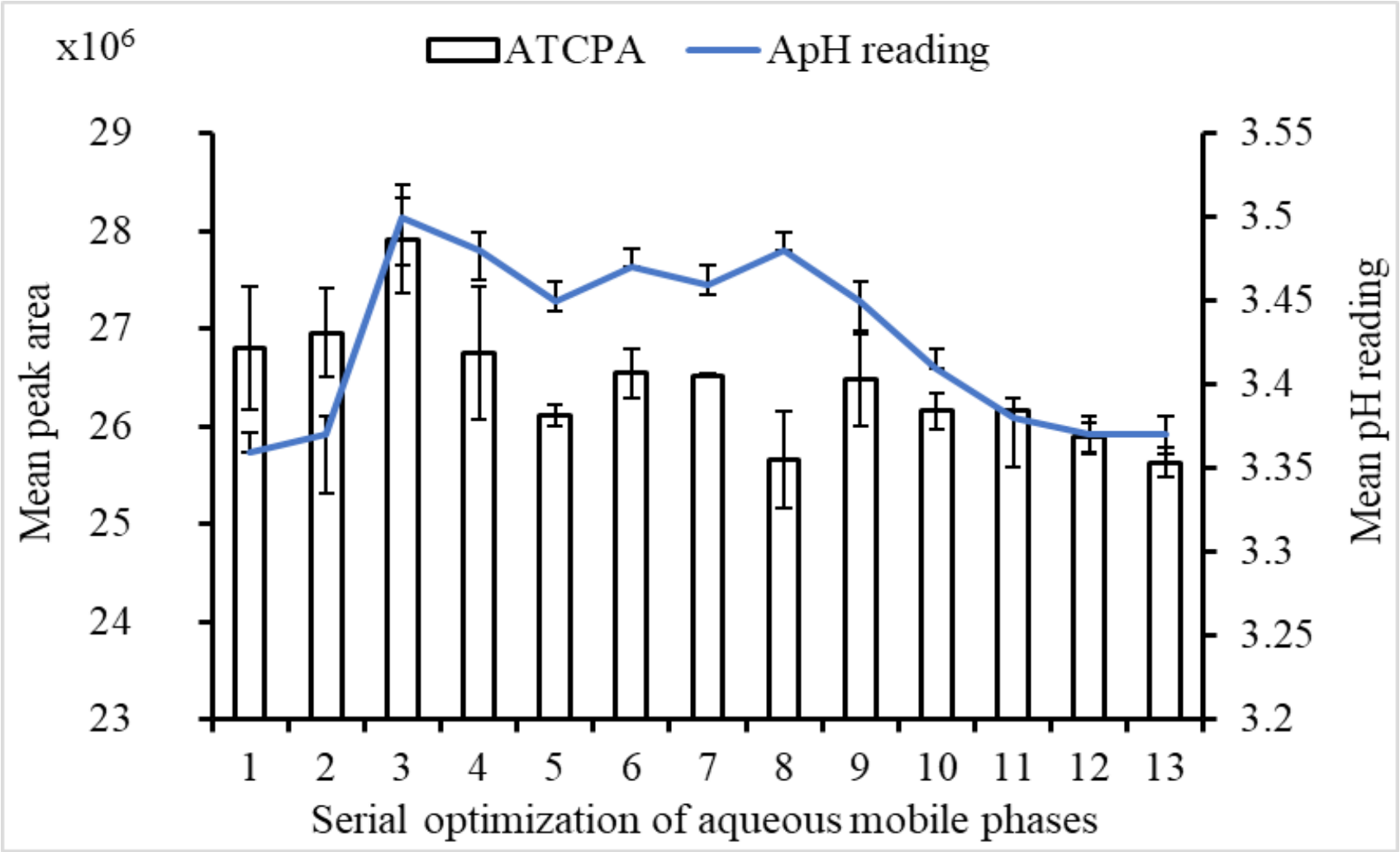

Figure 4: Comparative illustration for the optimization of the selected aqueous mobile phase by ATCPA and ApH readings

Table 4: The Instrumental responses for the optimization of the selected mobile phase

Solution	% ACN in Aqueous Mobile Phase	ApH reading ± STDEV	Organic Mobile Phase	ATCPA ± STDEV
1	H_2O + 0.1% FA + 0% ACN	3.36 ± 0.00	ACN + 0.1% FA	(27 ± 2) x 10^6
2	H_2O + 0.1% FA + 0.5% ACN	3.37 ± 0.08	ACN + 0.1% FA	(27 ± 1) x 10^6
3	H_2O + 0.1% FA + 1.0% ACN	3.50 ± 0.07	ACN + 0.1% FA	(28 ± 2) x 10^6
4	H_2O + 0.1% FA + 1.5% ACN	3.48 ± 0.04	ACN + 0.1% FA	(27 ± 2) x 10^6
5	H_2O + 0.1% FA + 2.0% ACN	3.45 ± 0.01	ACN + 0.1% FA	(261 ± 3) x 10^5
6	H_2O + 0.1% FA + 2.5% ACN	3.47 ± 0.00	ACN + 0.1% FA	(265 ± 6) x 10^5
7	H_2O + 0.1% FA + 3.0% ACN	3.46 ± 0.01	ACN + 0.1% FA	(2652 ± 4) x 10^4
8	H_2O + 0.1% FA + 3.5% ACN	3.48 ± 0.00	ACN + 0.1% FA	(26 ± 1) x 10^6
9	H_2O + 0.1% FA + 4.0% ACN	3.45 ± 0.04	ACN + 0.1% FA	(26 ± 1) x 10^6
10	H_2O + 0.1% FA + 4.5% ACN	3.41 ± 0.00	ACN + 0.1% FA	(262 ± 5) x 10^5
11	H_2O + 0.1% FA + 5.0% ACN	3.38 ± 0.07	ACN + 0.1% FA	26 x 10^6 ± 0
12	H_2O + 0.1% FA + 7.5% ACN	3.37 ± 0.03	ACN + 0.1% FA	(259 ± 4) x 10^5
13	H_2O + 0.1% FA + 10.0% ACN	3.37 ± 0.03	ACN + 0.1% FA	(256 ± 4) x 10^5

FA, formic acid; ApH, average pH reading; ATCPA, average total chromatographic peak area; STDEV, standard deviation

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