



Chemometrics Approach to QuEChERS-dSPE for Multi-Standard Determination of Pesticides in Blank Samples of Milli-Q-Water Using High-Performance Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS)

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ABSTRACT

The development of the best efficient technique for multi-pesticide determination in food samples is one of the best ways to address issues concerned with the use of pesticides in agricultural practices. Even though, several conventional techniques have been used earlier such as solid-phase extraction (SPE) and liquid phase microextraction (LPME), unfortunately, these treatment techniques possess poor sensitivity towards targeted analytes due to lack of modifications and optimization which provides an optimum condition for the analyses. In the present work however, chemometrics (multivariate) approach was used as response surface methodology (RSM) for optimising significant factors of quick, easy, cheap, effective, rugged and safe (QuEChERS) with the dispersive solid phase extraction (dSPE) technique. The Blanket-Burman (screening) and Box-Behnken (optimising) design generated by Minitab statistical software were used for the screening and optimisation of significant factors, respectively as well as quantification using total chromatographic peak areas (TCPA) responses of high-performance liquid chromatography-tandem mass spectrometry instrument. Eventually, the acquired average TCPA recovery (56%) for the RSM optimized QuEChERS-dSPE technique was favoured over that of default technique (44%) after comparative studies. This justifies the validity of the optimized method to play an important role in the determination of multi-pesticide residues in water and other food samples with higher matrix interferences.

Keywords: Chromatographic peak areas, Chemometrics RSM, LC-MS, Pesticide analytes, QuEChERS-dSPE

INTRODUCTION

Food crops are grown and protected with effective pesticides (Raven, 2014) for more than six decades to continue satisfying population and improve the health quality of life (Trostle, 2010). Unfortunately, the mishandlings in using the chemicals as well as their properties of higher molecular weight, lower vapour pressure, half-life ($t_{1/2}$) and solubility have led to their continuous accumulation in environmental water and moist soil (Lawal *et al.*, 2018c). Then, the pesticide eventually gets into the plants through the transportation medium from the roots to the other parts of the plant such as seeds, fruits and vegetables (Lawal & Koki, 2019). At the long run, the residual deposits of multiple pesticide residues result in many kinds of health-related issues that include birth defects, cancers and cardiovascular diseases (Lawal *et al.*, 2018a; Lawal *et al.*, 2018b). However, these issues can be addressed by the development of an efficient technique for the determination of multiple pesticide residues in various food samples. Conventional techniques for the sample preparations such as liquid-phase microextraction (LPME) and solid-phase extraction

(SPE) have been used previously (Lawal *et al.*, 2016) but the techniques lack sensitivity in targeting the analytes at lower concentration levels. It could be due to lack of modifications and optimization to provide an optimum condition for the analysis of targeted analytes.

The objective of this study is to develop a sample preparation technique by chemometrics approach (Montgomery, 2013) using response surface methodology (RSM) designs generated by Minitab statistical software for the screening (Blanket-Burman) and optimizing (Box-Behnken) the significant factors (0.05-0.26 statistical limits) associated with quick, easy, cheap, effective, rugged and safe (QuEChERS) coupled with the dispersive solid-phase extraction (dSPE) technique. Moreover, the QuEChERS-dSPE technique is excellently known for its cleanup ability (Anastassiades *et al.*, 2003; Gunatilake *et al.*, 2014). Thus, the multi-pesticides (Dursban, Diazinon, Thiamethoxam, Metalaxyl, Thiobencarb, Baycarb, Carbaryl and Propamocarb) standard solution were analyzed for the optimization as documented (Lawal & Koki, 2019).

The quantitative analysis involved the use of total chromatographic peak areas (TCPA) responses of high-performance liquid chromatography-tandem mass spectrometry (Agilent G6490A LC-MS/MS) instrument runs for the screening and optimizing significant factors of the sample preparation method.

It is hoped that the developed sample preparation method could provide better results of the analyte accuracies and precisions and be used as a reference guide for the routine determination of multiple pesticide residues in water and other food samples with higher matrix interferences coupled with the used of advanced instruments to know the concentration levels of multiple pesticides residue for better environmental and food safety (Lawal *et al.*, 2016).

MATERIALS AND METHODS

Sampling and treatments

The stock standard solution of pesticides (100 mg/kg) for Dursban, Diazinon, Thiamethoxam, Metalaxyl, Thiobencarb, Baycarb, Carbaryl and Propamocarb were purchased from AccuStandard® (New Haven, USA). The stock solutions were singly diluted to 1 mg/kg standard working solutions using the estimated volume of

methanol and preserved in a refrigerator at 4 °C. The ProElut™ AOAC 2007.01 QuEChERS and d-SPE kits for the general sample of vegetables and fruits were purchased from Dikma Technologies Inc. (Lake Forest, USA). The LC-MS/HPLC grade organic solvents, which include methanol and acetonitrile (ACN) purchased from Merck (Germany). The acetic and formic acid (FA) were purchased from Fisher Scientific. The Millipore-filtered (deionized) water was obtained using Merck Millipore water purification system (Billerica, USA).

Conditioning of the LC-MS/MS instrument

The prepared 1 mg/kg working standard solution of the eight pesticides mixture was used for the Mass-Hunter and auto-tuning optimisation of the Triple quadrupole LC/MS (G6490A) instrument (Agilent Technologies, Singapore). The instrument is built in electrosprays ionisation (ESI ±) MS/MS sensitivity and Jet stream technology. The auto-optimization generated total ion chromatography (TIC) (Fig. 1). Other parameters that supported the MRM scan include analytes' precursor ions, product ions (qualifier and quantifier) with their respective collision energies (Table 1).

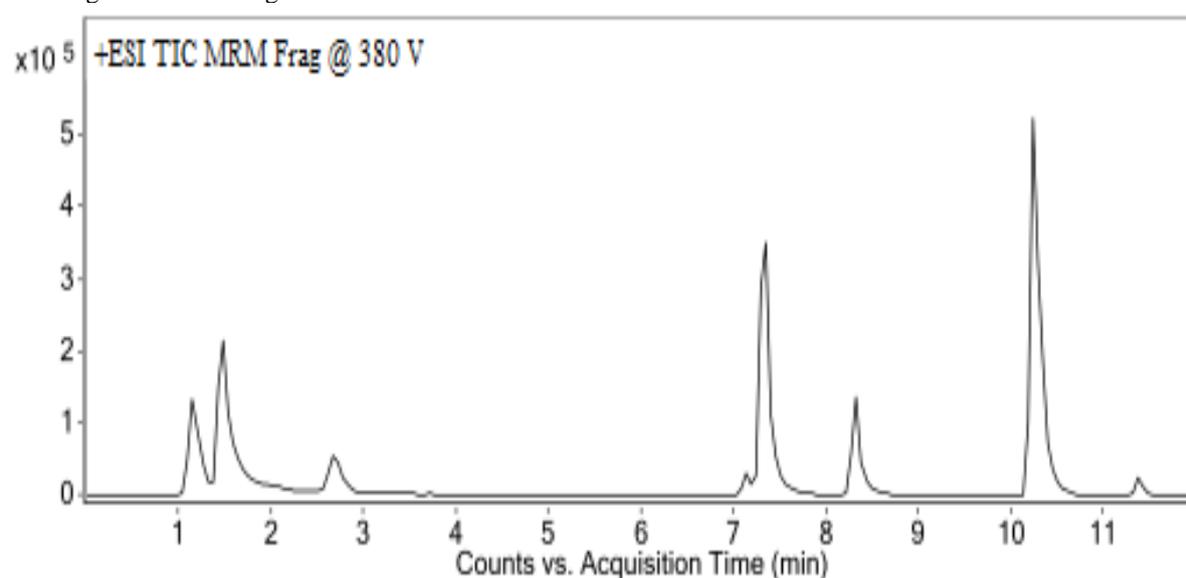


Fig. 1: Total ion chromatography (TIC) chart for the multiple pesticides analyzed

Table 1: The Mass-Hunter and auto-tuned optimisation for the setup of the LC-MS/MS instrument

TIC	Pesticides	Molecular Formula	Ionization Mode	Precursor Ion, m/z	Product Ions (m/z)	Collision Energies (eV)	RT ₁ ;RT ₂ (min)
1	Propamocarb	C ₉ H ₂₀ N ₂ O ₂	[M+H] ⁺	189	74;102	26;14	1.36;1.36
2	Carbaryl	C ₁₂ H ₁₁ NO ₂	[M+H] ⁺	202	127;145	30;6	7.16;7.16
3	Baycarb	C ₁₂ H ₁₇ NO ₂	[M+H] ⁺	208	77;95	42;10	8.34;8.34
4	Thiobencarb	C ₁₂ H ₁₆ CINOS	[M+H] ⁺	258	89;125	54;26	10.34;10.34
5	Metalaxyl	C ₁₅ H ₂₁ NO ₄	[M+H] ⁺	280	160;220	26;10	7.33;7.33
6	Thiamethoxam	C ₈ H ₁₀ CIN ₅ O ₃ S	[M+H] ⁺	292	132;211	26;10	2.68;2.68
7	Diazinon	C ₁₂ H ₂₁ N ₂ O ₃ PS	[M+H] ⁺	305	97;169	42;22	10.22;10.22
8	Dursban	C ₉ H ₁₁ C ₁₃ NO ₃ PS	[M+H] ⁺	350	97;198	34;22	11.36;11.36

Key: TIC, total ion chromatography; RT, retention time

Afterwards, the multi-standard pesticides solution was analyzed using the optimised LC-MS/MS instrument, which is operated at 15% starting organic mobile phase B (ACN + 0.1% FA) coupled with mobile phase A (deionized H₂O + 0.1% FA + 1% ACN) pushed by a stream of nitrogen gas. The 5 µL analyte solution was injected, passed and ran through Supelco HPLC column [Ascentis® Express C₁₈ (5 cm x 2.1 mm, 2.7 µm)] (Sigma-Aldrich, USA) at 30 °C and flow rate of 0.1 mL/min. The gradient path was estimated: 0 – 1.6 min, 15% B; 1.6 - 10.4 min, 15 – 100% B; 10.4 – 12.0 min, 15% B. Apparently, all experimental runs took place after attainment of good acquisition for a conducive instrumental conditions such as stabilized gas flow, nebulizer, temperature and capillary voltage.

The Default and RSM Optimization of QuEChERS-dSPE Sample Preparation Method

The default, screening and optimizing factors of QuEChERS extraction and cleanup methods were carried out using blank samples of Milli-Q-water because of its low matrix interferences and slow putrifaction property as compared to other food samples. Therefore, the comparative studies was carried out to know the QuEChERS-dSPE method that would yield higher average TCPA (ATCPA) of analyte recoveries from LC-MS/MS analysis which is an index that corresponds to the amount of analytes present in the analysed samples (Lawal *et al.*, 2018b).

The procedure for the default QuEChERS-dSPE method was carried out as revealed by Agilent (2011) and DIKMA (2016) was employed for QuEChERS-dSPE analysis. Experimentally, 10 mL blank sample was measured in 50 mL centrifuge tube. 1 % acetic acid (HOAc) in 15 mL ACN was added after spiking the content with 200 µL of 0.1 mg/kg multi-pesticides mixture of

standard solutions. The tube was covered and vortexed for 1 min before addition of a sachet of QuEChERS extraction salt. The tube was covered and shaken vigorously for 1 min and centrifuged at 4000 rpm for 5 min. Then, 0.5 mL supernatant (ACN extract) was transferred into 2 mL centrifuge tube containing a sachet of the cleanup agent. The tube was vortexed for 30 s before centrifugation at 4000 rpm for 5 min. Then, 80 µL of ACN extract was mixed with Milli-Q-water (1:5) in 2 mL HPLC auto-sampler vial and vortexed (1 min) before LC-MS/MS instrumentation. Meanwhile, the RSM screening and optimization of factors associated with QuEChERS-dSPE technique were carried out using Plackett-Burman (P-B) and Box-Behnken (B-B) designs, respectively.

Hence, both designs runs were involved in the use of TCPA responses resulted from the analyses of the 200 µL of 0.1 mg/kg spiked mixture of standard pesticide solutions on the blank sample of Milli-Q-water. However, the essential factors and levels (Table 2) considered for the QuEChERS-d-SPE RSM optimization were factors associated with the acid/base (pH) of the extraction solvent and the mechanical setups such as centrifugation speed and centrifugation time in both the extraction and cleanup stages. Because the previous reported RSM optimisation of QuEChERS-dSPE method influences the used of sorbent materials such as primary secondary amine (PSA), octa-dodecyl bonded silica (C₁₈), graphitised carbon black (GCB), and sodium acetate (NaOAc) salts (Li *et al.*, 2016; Melo *et al.*, 2013; Rai *et al.*, 2016; Rizzetti *et al.*, 2016). Therefore, the methodological approach for the RSM optimization of the QuEChERS-dSPE was carried out similarly to the default procedure above except with different values for the selected factors screened and optimized.

Table 2: The 2-Level Factors used in P-B design for QuEChERS-dSPE

S/N	Factors	Levels	
		Low (-)	High (+)
1	Quantity of Milli-Q-water (sample) for QuEChERS extraction (mL)	6.7	13.3
2	Percentage of HOAc in 15 mL of ACN (%)	0	2
3	Centrifugation speed for QuEChERS extraction (rpm)	1000	7000
4	QuEChERS extraction time (min)	2	8
5	Centrifugation speed for d-SPE (rpm)	1000	7000
6	Cleanup time for d-SPE (min)	2	8

Later on, the statistical software was used to generate the experimental designs with 12 runs as reported by Vidal *et al.* (2007). The screening runs were carried out to analyze the significant factors at 2-level each and 74% confidence interval (0.26 significant level). It is because all the six analyzed factors of the QuEChERS-dSPE method

were statistically insignificant at the usual 0.05 but were significant at 0.26 significant level. Subsequently, the significance factors (Table 3) at three levels each underwent optimization using B-B design with 15 runs at 3 centre points without a replicate was generated by the statistical software.

Table 3: The 3-Level significant Factors of QuEChERS-dSPE method

S/N	Factors	Levels		
		Low (-)	Medium (0)	High (+)
1.	Quantity of sample for QuEChERS extraction (mL)	6.7	10	13.3
2.	Percentage of HOAc in 15 mL of ACN (%)	0	1	2
3.	QuEChERS extraction time (min)	2	5	8

The Comparative Studies of Default and RSM Optimized QuEChERS-dSPE Technique

The default and RSM optimized QuEChERS-dSPE techniques were compared based on the resulted ATCPA analyzed in triplicates after spiking the blank sample with 200 μ L of 0.1 mg/kg multi-pesticides mixture of standard solutions. Accordingly, the better method with higher ATCPA (analyte recoveries) could be used to provide better results of the analyte accuracies and precisions for the routine

determination of multiple pesticide residues in water and other samples of food.

RESULTS AND DISCUSSION

RSM Screened and Optimized Significant Factors of QuEChERS-dSPE Method

Plackett-Burman Screening

Table 4 shows the Plackett-Burman designs with 12 runs use to screened the significant factors.

Table 4: P-B design responses for screening 6-factors of QuEChERS-dSPE

Run Order	A (mL)	B (%)	C (rpm)	D (min)	E (rpm)	F (min)	TCPA
1	13.3	0	7000	2	1000	2	305490
2	13.3	2	1000	8	1000	2	357928
3	6.7	2	7000	2	7000	2	375391
4	13.3	0	7000	8	1000	8	464061
5	13.3	2	1000	8	7000	2	383030
6	13.3	2	7000	2	7000	8	364323
7	6.7	2	7000	8	1000	8	382003
8	6.7	0	7000	8	7000	2	461944
9	6.7	0	1000	8	7000	8	457133
10	13.3	0	1000	2	7000	8	432234
11	6.7	2	1000	2	1000	8	369337
12	6.7	0	1000	2	1000	2	455224

Key: A, sample quantity for QuEChERS extraction; B, % HOAc in 15 ml of ACN; C, QuEChERS extraction centrifugation speed; D, QuEChERS extraction time; E, centrifugation speed for d-SPE; F, cleanup time for d-SPE

The P-B design screening carried on QuEChERS-dSPE method is in accordance with the documentation of Fang *et al.* (2017). But the RSM screening carried out for this research indicated significant factors that include sample quantity, the percentage of HOAc in 15 mL of

ACN and extraction time as illustrated by the Pareto chart (Fig. 2). Notably, the Pareto chart of standardized effects is an illustration of horizontal bars for the screened factors and the red vertical line across the bars indicates the level of significant difference.

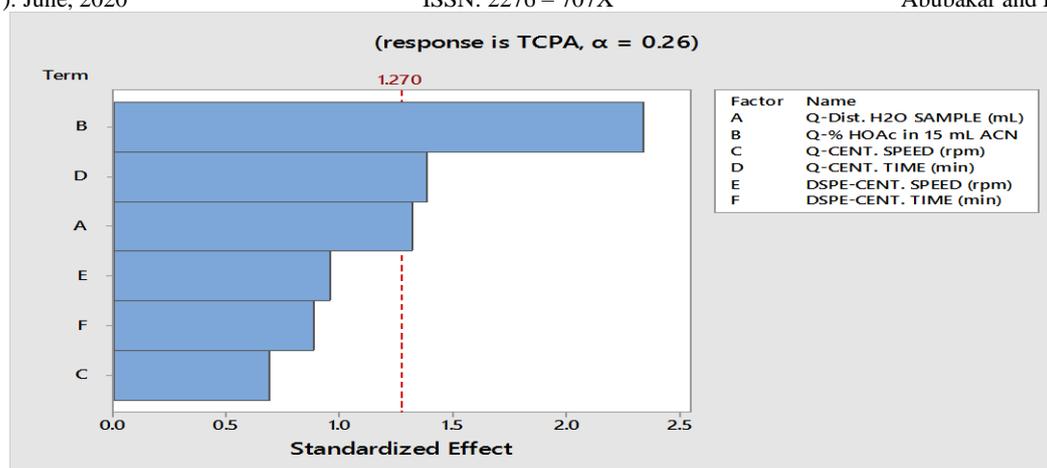


Fig. 2: Pareto chart of P-B design showing the screened factors of QuEChERS-dSPE

Box-Behnken Optimization

All the 15 experimental runs carried out (Table 5) were successful for optimization of the screened

factors of the QuEChERS-dSPE method as represented by A, B and C.

Table 5: B-B design responses for the 3-significant factors of QuEChERS-dSPE

Run Order	Point Type	A (mL)	B (%)	C (min)	TCPA
1	2	6.7	0	5	468556
2	2	13.3	0	5	597884
3	2	6.7	2	5	441682
4	2	13.3	2	5	497001
5	2	6.7	1	2	579964
6	2	13.3	1	2	490067
7	2	6.7	1	8	537592
8	2	13.3	1	8	493233
9	2	10	0	2	523942
10	2	10	2	2	460280
11	2	10	0	8	389043
12	2	10	2	8	423322
13	0	10	1	5	474820
14	0	10	1	5	467664
15	0	10	1	5	468895

Key: A, quantity of sample (Milli-Q-water) for QuEChERS extraction; B, % HOAc in 15 ml of ACN; C, QuEChERS extraction time; TCPA, total chromatographic peak area

The surface plots (Fig. 3) illustrated the response surfaces that respectively resulted in the best (optimized) condition to yields more of TCPA collectively when the insignificant factors were set

up at a medium level. Moreover, the highest spot on the three-dimensional response view of the surface plot signified the best-optimized value that could provide the maximum TCPA.

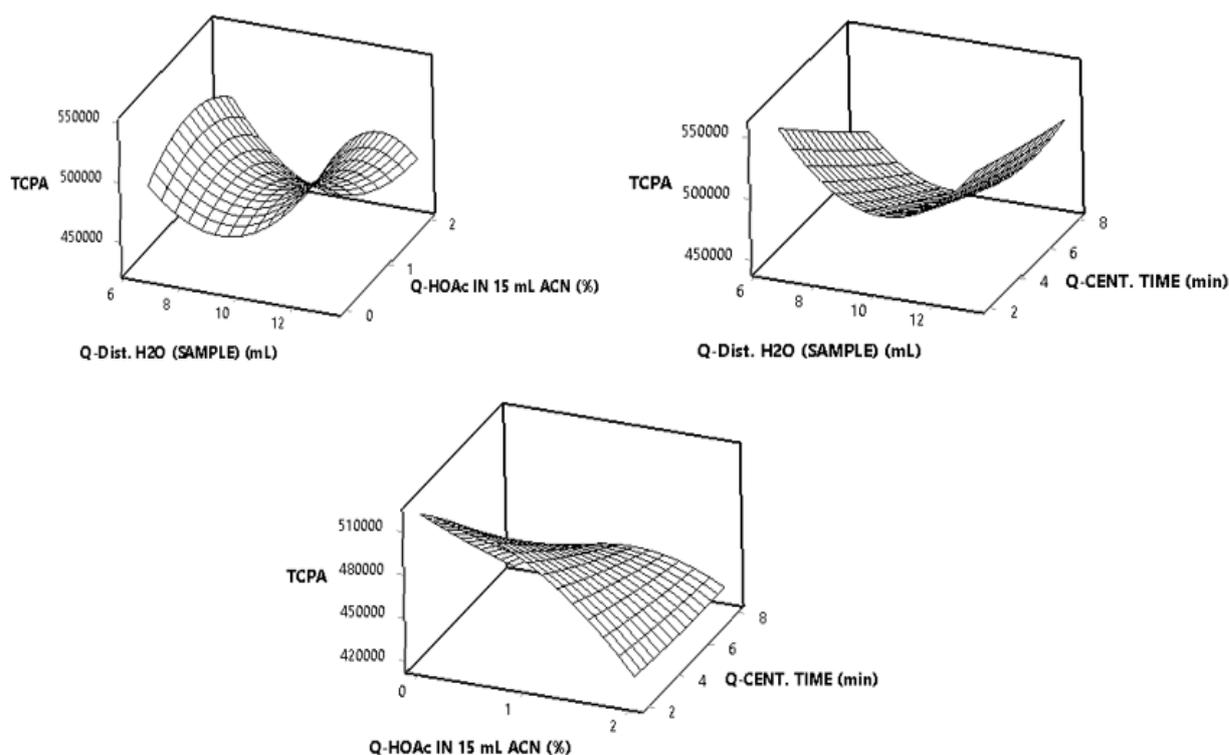


Fig. 3: The highest TCPAs attained on Surface Plot for the interacted significant factors

The optimized factor levels were illustrated (Fig. 4) by the response optimizer that provided the

optimum desirability corresponding to TCPA of the pesticide analytes.

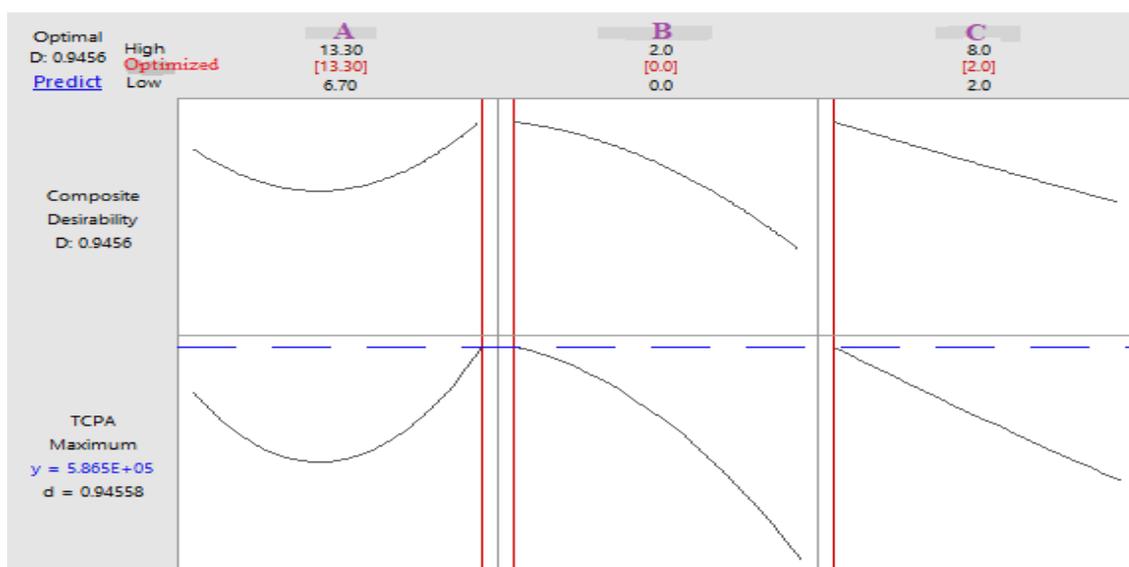


Fig. 4: The B-B response optimized chart for 3-significant factors of QuEChERS-dSPE

The RSM optimized values are 13.3 mL (≈ 20 g fresh fruit) quantity of sample, 0 % HOAc in 15 mL of ACN, and 2 min of QuEChERS extraction time. The results suggested the use of 0 % HOAc in 15 mL of ACN, which is less than the commonly used 1 % HOAc in 15 mL of ACN for the analysis of pesticides, bio-pesticides and agrochemicals (Golge & Kabak, 2015; Jadhav *et*

al., 2015; Romero-González *et al.*, 2014). It could be as a result of high acidic medium (pH) of the default prepared sample (5.37 ± 0.04) coupled with the high pH of the mobile phase A (3.68 ± 0.06) and B (6.56 ± 0.02) which could have diminished the recovery of the analytes. While the pH of the RSM optimized prepared sample (8.33 ± 0.01) coupled with the mobile phases A and B setup

resulted in the higher recovery of analytes. The result agrees with the documentation of Georgakopoulos and Skandamis (2011). Moreover, the optimized setup favours the reduction of QuEChERS centrifugation time from 5 (default) to 2 min, which essentially increases the rapidness of the QuEChERS extraction (Abdulra'uf *et al.*, 2019; Hepperle *et al.*, 2015).

Both improved and default setup of QuEChERS-dSPE methods were compared based on their ATCPA obtained from the analysis of 0.1 mg/kg multi-pesticides mixture of the standard solution. The data of the comparative studies (ATCPA \pm RSD %) shows that the modified method was favoured by 56% (76904 \pm 4.12) over the default 44% (60239 \pm 3.23) QuEChERS-dSPE method. Notably, the optimized QuEChERS-dSPE technique is considered valid because it is experimentally (practically) significant by improving the ATCPA (56 %) recoveries after the comparative studies with the default method (44 %).

CONCLUSIONS

The RSM optimization of the default QuEChERS-dSPE sample treatment methods was successfully carried out. The screened factors of the optimized QuEChERS-dSPE method were significant at 0.26 statistical level. However, the optimized method was experimentally reliable after comparative studies between the default and RSM optimized QuEChERS-dSPE method. Moreover, the result would yields higher recovery (ATCPA) of the multiple pesticides in the homogenized matrix samples. Therefore, the developed method could be reliable for routine multi-pesticide residues determination in various food samples coupled with the use of LC-MS/MS instrument.

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