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Validation of QuEChERS Based LC-MS/MS Determination Method for The Analysis of Some Neonicotinoid Insecticide Residues in Tomato Samples

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Abstract: In this study, we aimed to validate the analytical procedure for the multiple residue analysis of imidacloprid, acetamiprid, thiamethoxam, clothianidin and thiacloprid in tomatoes. For this purpose, tomato samples were extracted and cleaned-up by using QuEChERS method. Chromatographic analyses were performed with LC-MS/MS. The method was validated according to the limit of detection (LOD), linearity, accuracy and recovery The linearity of five pesticides were determined with the range of 5-150 µg L^{-1}. The correlation coefficients (r^2) range from 0.992 to 0.996. The LODs were between 1.03 and 1.22 µg kg^{-1}. The limits of quantification (LOQ) varied between 3.44 and 4.07 µg kg^{-1}. The recovery of fortified tomato samples in five different neonicotinoid groups of insecticides at two different concentrations (10 µg kg^{-1}, 50 µg kg^{-1}) were conducted. For repeatability, the relative standard deviation (RSD%) ranged from 0.84 to 5.43, and for reproducibility, RSD% ranged from 4.58 to 15.15. The overall recovery of the method was 102.52% and the RSD was 9.79% (n = 300). All results were compatible with the values specified in SANTE (2017) for recovery (70–120%) and repeatability (RSD% ≤ 20%).

Key words: *LC-MS/MS, method validation, neonicotinoid, pesticide residue, QuEChERS*

Domates Numunelerinde Bazı Neonicotinoid Grubu İnsektisit Kalıntılarının Saptanmasında QuEChERS ve LC-MS/MS Metodunun Validasyonu

Öz: Yapılan bu çalışmada, domateste imidacloprid, acetamiprid, thiamethoxam, clothianidin ve thiacloprid çoklu kalıntı analizi için analiz prosedürünün valide edilmesi amaçlanmıştır. Bu amaçla domates örnekleri QuEChERS yöntemi ile ekstrakte edilerek LC-MS/MS cihazında analiz edilmiştir. Metot; tespit ve ölçüm limiti, doğrusallık ve doğruluk (tekrarlanabilirlik, tekrar üretilebilirlik, geri kazanma) limitine göre değerlendirilmiştir. Yöntemde beş pestisit için 5-150 µg L^{-1} aralığında doğrusallık saptanmıştır. Korelasyon katsayıları 0.992- 0.996, tespit limitleri (LOD) ise 1.03 ve 1.22 µg kg^{-1} arasında belirlenmiştir. Ölçüm limiti (LOQ) 3.44 ve 4.07 µg kg^{-1} arasındadır. Geri alım çalışmaları için domates örnekleri beş neonikotinoid grubu insektisit ile iki farklı konsantrasyon (10 µg kg^{-1}, 50 µg kg^{-1}) seviyesinde zenginleştirilmiştir. Tekrarlanabilirlik için, relatif standart sapma (RSD%) 0.84 ile 5.43 arasında, tekrar üretilebilirlik için (RSD%), 4.58 ile 15.15 arasında değişmiştir. Tüm metodun geri alımı %102.52, RSD ise %9.79 olarak bulunmuştur (n=300). Tüm bulgular SANTE (2017) 'de belirtilen geri alım sınırlarına (%70-120) ve kesinlik kabul oranı için belirtilen değerlere (%RSD ≤ %20) uygundur.

Anahtar kelimeler: LC-MS/MS, metod validasyonu, neonicotinoid, pestisit kalıntısı, QuEChERS

1. Introduction

Pesticides are widely used in agriculture to increase yield and quality and to extend the life of stored foods (Ecobichon 2001). Pesticide residues on foods after pesticide application may pose a risk to food safety in human nutrition. Pesticides can also spread to water, soil and air, causing instability in the ecosystem (Amadeo and Juan 2008). For all these reasons, it is important to monitor the persistence of pesticide residues in food for human health, the environment and international trade.

Neonicotinoids are the most widely used insecticides in the world. This group includes imidacloprid, thiamethoxam, acetamiprid, thiacloprid, nitenpyram, clothianidin and dinotefuran. They have reached a share of around 25% in the global pesticide market, with a monetary value of around $ 2.63 billion (Jeschke et al. 2011).

They are highly effective insecticides that control many important pests (Nauen et al. 2008; Jeschke et al. 2011). They have been used effectively against the various kinds of insect pests by different treatments in more than 120 countries for 25 years (Nauen et al. 2008; Bass et al. 2015). These pesticide were widely used among farmers due to the many pesticide application methods (foliar sprays to plants, soil drench, seed treatment and seedling dip) (Suganthi and Bhuvaneswari 2018). Neonicotinoids are mainly applied in cotton, vegetable and fruit plantations.

These systemic pesticides are difficult to remove by ultraviolet light degradation, wash off and ozonization (Suganthi and Bhuvaneswari 2018). In this respect, neonicotinoid residues on agricultural products pose a risk to consumer health. Cimino et al. (2017) in their review of the direct effects of neonicotinoids on human health, stated that they may cause developmental and neurological disorders, tetralogy of fallot, anensephaly, autism, spectrum disorders, memory loss and finger tremor symptoms.

Durmaz and Tiryaki (2018) stated that the method validation means that method developed for any sample matrix for pesticide residue analysis is validated in the laboratory to confirm that it is accurate. Method validity needs to be verified to some criteria. After verification, the analysis starts with real samples. Even if an analysis procedure is validated in the international literature, that procedure may not give the same result in the laboratory. Validation parameter values of a method cannot be copied from literature or other laboratories. Even if a method is the official method of AOAC (Association of Official Analytical Chemists), the method validation parameter values of that method should be determined and comply with SANTE (2017) limits (Tiryaki 2017).

Turkish Food Codex Regulation of Maximum Residue Limits of Pesticides has determined the application procedures and principles of the maximum residual limits of pesticides that are allowed to be found in plant and animal foods in order to ensure the high level of consumer protection in our country (Anonymous 2016). This regulation can only be applied if there are appropriate methods for determining and monitoring residue limits. This research was conducted to support the implementation of the regulation. In this study, it was aimed to validate the analysis procedure for multiple residue analysis of imidacloprid, acetamiprid, thiamethoxam, clothianidin and thiacloprid used for pest control in tomato.

2. Materials and Methods

2.1. Chemicals and solvents

Pesticide reference standards (Acetamiprid, Imidacloprid, Thiametoxam, Clothianidin and Thiacloprid) were taken from Dr. Ehrenstorfer GmbH (Bgm.-Schlosser-STr. 6A, Augsburg, Germany). Acetonitrile (MeCN), methanol (MeOH), Magnesium sulfate anhydrous ($MgSO_4$), sodium acetate (NaOAc) and acetic acid (AcOH) were taken from Merck (Darmstadt, Germany). Primary-secondary amine (PSA) was taken from Supelco Analytical (595 N Harrison Rd, Bellefonte, PA, USA).

2.2. Device and tools

In the study, LC-MS/MS (Shimadzu LC-MS/MS-8050), centrifuge (Hettich Rotina 380, 50 mL and Hettich Universal 320R, suitable for 15 mL centrifuge tube), precision bascule (Shimadzu AUW220D, ±0.0001 g), industrial grinder (Empero), Vortex (Ika) were used. Also, micropipette, syringe, 50 mL falkon tubes, washing bottle, ultrasonic bath, 2 and 12 mL glass vials with screw cap, 5 mL syringes, 45/25 mm syringe filters, baloon joje, disposable pipette and various materials such as weighing container were used in the analysis.

2.3. Extraction of samples, clean-up and fortification

Extraction in residue analysis was performed with the QUECHERS (Quick, Easy, Cheap, Rugged, Safe) multiple residue analysis method developed by Anastassiades et al. (2003). The method essentially comprises the steps of extraction and cleaning of the matrix (Figure 1). 1 kg (minimum of 10 pieces) samples (EC 2002) were all homogenized with a grinder, weighed 15 grams of homogenized sample, transferred to a 50 mL centrifuge tube. MeCN (acetonitrile) containing 15 mL 1% AcOH (acetic acid), 6 g $MgSO_4$ (dehydrated magnesium sulfate) and 1.5 g of NaOAc (dehydrated sodium acetate) were added on it. The closed centrifuge tube was placed in the centrifuge by shaking rapidly for 1 minute and centrifuged at 5000 rpm speed for 5 minutes and extraction was completed (Lehotay et al. 2005).

After this process, 8 mL of the liquid (supernatant) formed on the solids which had settled to the bottom in a 50 mL centrifuge tube was taken and this liquid were added to a 15 mL centrifuge tube included 1.2 g of magnesium sulfate and 0.4 g of PSA. The tube was shaken for about 1 minute and centrifuged at 5000 rpm for 5 minutes (Lehotay et al. 2005). After this process, it was ensured that the substances other than the analyte were cleaned. The liquid formed after centrifugation was removed by syringe, filtered and placed into 2 mL glass vials for liquid chromatography.

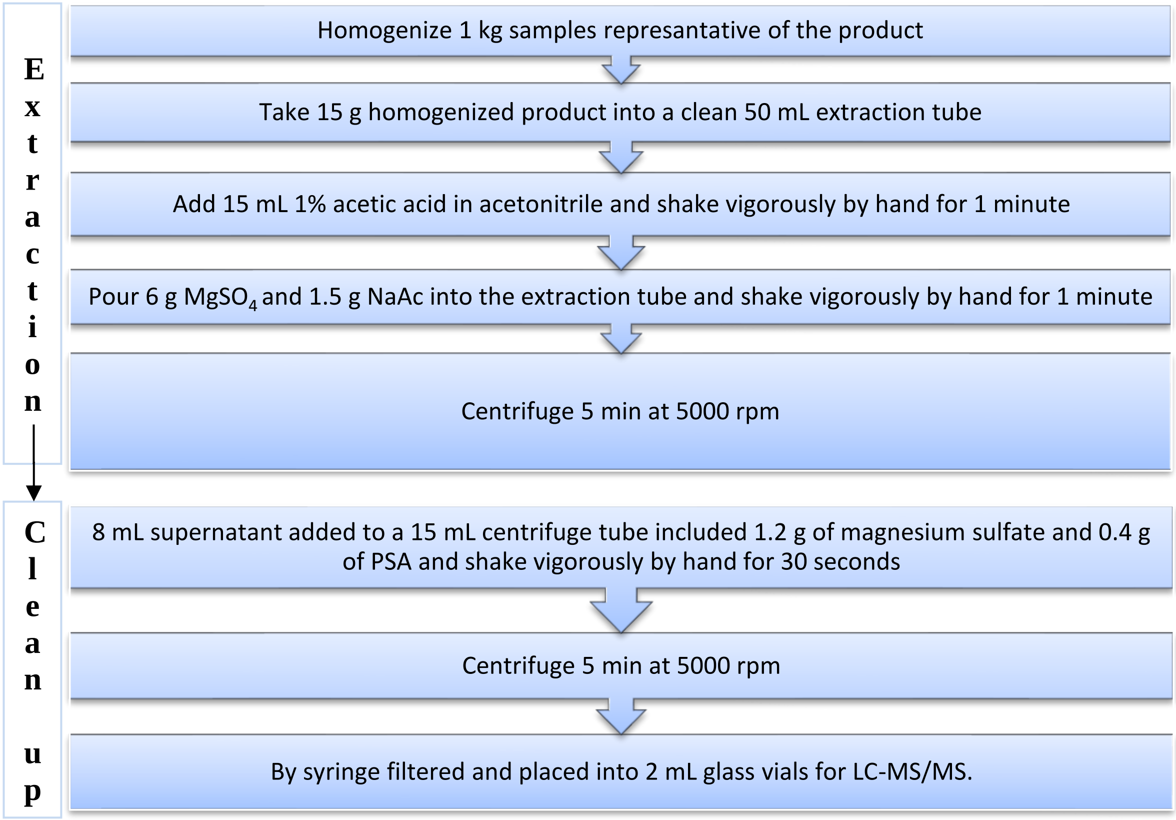

Figure 1. Analytical steps of the QuEChERS-AOAC Official Method 2007.01 for the analysis of acetamiprid, imidacloprid, thiametoxam, clothianidin and thiacloprid in tomato samples

Şekil 1*. Domates örneklerinde acetamiprid, imidacloprid, thiametoxam, clothianidin ve thiacloprid analizi için QuEChERS-AOAC Resmi Metodu 2007.01'nun analitik basamakları*

Validation studies were performed with spiked tomato samples. 1 kg (minimum of 10 pieces) Pesticide-free samples were all homogenized. 15 g analytical portion of the homogenized tomato sample was placed in a falcon tube. According to Dankyi et al. (2014) and Banerjee et al. (2019) two (10 μg kg^{-1} and 50 μg kg^{-1}) different spiking levels were added to the homogenized tomato. Fortification pattern are summerized in Table 1.

The control sample without pesticide was analyzed in three replicates.

2.4. Chromatographic conditions

Chromatographic analyzes were performed using LC-MS/MS (Liquid Chromatography / Tandem Mass Spectrometer) (Tokat Gaziosmanpaşa University Scientific and Technological Research Application and Research Center, Food Detection and Residue Analysis Unit, Food Residue Analysis Laboratory). The operating conditions of the device are given in Table 2.

Table 1. Fortification levels of tomato samples

Çizelge 1. *Domates örneklerinin fortifikasyon düzeyleri*

Fortification level	Acetamiprid (µg kg^{-1})	Clothianidin (µg kg^{-1})	Imidacloprid (µg kg^{-1})	Thiacloprid (µg kg^{-1})	Thiamethoxam (µg kg^{-1})
Level 1	10	10	10	10	10
Level 2	50	50	50	50	50
Control	-	-	-	-	-
EU-MRL	200	40	500	500	200

Table 2. Chromatographic conditions

Çizelge 2. *Kromatografik koşullar*

LC- MS/MS	Shimadzu 8050		
Mobile Phase A	Distilled water + 5 mmol ammonium acetate		
Mobile Phase B	Methanol + 5 mmol ammonium acetate		
Mobile Phase Flow	0.4 mL/min		
Column	C18 Inertsil ODS-4; 3 µm; 2.1 x 150 mm		
Gradient	Time (min)	%A	%B
	0-4	95	5
	4.01-6	5	95
	6.01-10	95	5
Column oven Temperature	35°C		
Injection Volume	5 µl		
MS Gas Temperature	300°C		
MS Gas Flow	10 L/min		
Nebulizer Pressure	270 kPa		
Room Temperature	20°C		

3. Results and Discussion

Performance characteristics of the method were determined by evaluating linearity, accuracy, detection limit and measurement limits. MS parameters for the five neonicotinoids analyzed are given in Table 3. Chromatogram of neonicotinoid spiked (100 µg kg^{-1}) tomato sample are given in Figure 1.

Table 3. Precursor ion (m/z), product ion (m/z) and collision energies of neonicotinoids

Çizelge 3. *Neonikotinoidlerin ana iyon kütleleri, ürün iyon kütleleri ve çarpışma enerjileri*

Pesticides	Precursor ion (g mol^{-1})	Product ion (g mol^{-1})	Collision energies (eV)
Acetamiprid	222.90	72.50/99.00 / 126.10	-53.0/-39.0 /-19.0
Clothianidin	249.80	132.00 / 169.10	-16.0 /-12.0
Imidacloprid	255.90	175.10 / 209.10	-19.0 /-16.0
Thiacloprid	252.80	90.10 / 126.00	-40.0 /-20.0
Thiamethoxam	291.80	181.10 / 211.20	-22.0 /-13.0

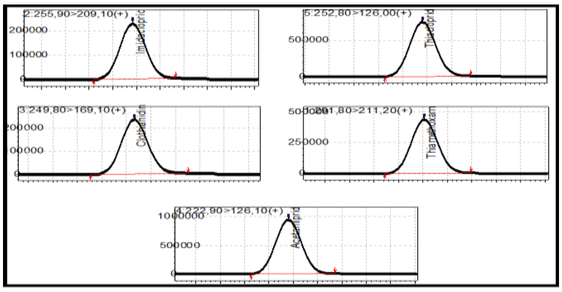

Figure. 1. Chromatograms obtained from tomato samples spiked with standard solutions

Şekil 1. *Standart çözeltilerle zenginleştirilmiş domates örneklerinden elde edilen kromatogramlar*

3.1. Linearity

Calibration points for all five active substances were prepared in a matrix-compatible manner with a final concentration of 1, 5, 10, 25, 50, 75,100 and 150 µg/L. Each calibration point was obtained by 3 repeated injections. The correlation coefficients (r^2) of the calibrations of all pesticides studied were above 0.99 (Table 4). This result shows that the method was linear with a specified concentration ranges.

Table 4. Correlation coefficients of calibration curves

Çizelge 4. *Kalibrasyon eğrilerine ait korelasyon kat sayıları*

Pesticides	Correlation coefficient (r^2)
Acetamiprid	0.9926831
Clothianidin	0.9959596
Imidacloprid	0.9969930
Thiacloprid	0.9968237
Thiamethoxam	0.9965715

3.2. Accuracy

Accuracy is a parameter that covers the parameters of trueness (recovery) and certainty (repeatability and reproducibility). The repeatability studies were performed with 3 injections at 2 different concentrations (10 and 50 µg kg^{-1}) on the same day (Table 5).

The intra-laboratory reproducibility studies were performed with 3 injections at 2 different concentrations at five different times (Table 6).

Table 5. For repeatability; % mean recovery, SD and RSD%

Çizelge 5. *Tekrarlanabilirlik için; % ortalama geri alım, standart sapma, % relatif standart sapma (%RSD) değerleri*

Pesticides		Spiking level, µg kg^{-1}					
		10			50		
		% Average recovery	SD	RSD%	% Average recovery	SD	RSD%
Acetamiprid	1	112.5	0.61	5.43	111.2	0.66	1.18
	2	110.2	0.45	4.12	108.6	1.07	1.96
Clothianidin	1	103.6	0.27	2.61	105.7	0.54	1.02
	2	103.4	0.26	2.48	107.1	1.22	2.28
Imidacloprid	1	94.2	0.09	0.97	98.2	0.41	0.84
	2	94.2	0.18	1.86	100.8	0.68	1.35
Thiacloprid	1	97.4	0.36	3.67	104.0	0.60	1.16
	2	90.3	0.18	2.02	102.3	0.62	1.21
Thiamethoxam	1	97.5	0.28	2.84	105.0	0.61	1.16
	2	92.6	0.18	1.91	102.4	0.84	1.64

In the repeatability studies, the pesticide recovery rates were between 92.60% and 112.50%, and RSD was between 0.84 and 5.43 (n = 150). In reproducibility studies, pesticide recovery rates were 88.24% to 113.23% and RSD was found to be 4.58 to 15.15 (n = 150). For the recovery asssesment, general overall the method recovery must be calculated (Polat and Tiryaki, 2019). The total recovery of the whole method was 102.52% and RSD was 9.79% (n = 300). All findings are suitable with the required recovery limits (70-120%) and the values specified for the certainty acceptance rate (RSD% ≤ 20%).

Table 6. For reproducibility; % Mean recovery, SD and RSD%

Çizelge 6. *Tekrarüretilebilirlik için; % ortalama geri alım, standart sapma, % relatif standart sapma (%RSD) değerleri*

Pesticides	**Spiking level, µg kg^{-1}**					
	10			**50**		
	% Average recovery	**SD**	**RSD%**	**% Average recovery**	**SD**	**RSD%**
Acetamiprid	111.11	0.68	6.15	112.10	3.4	6.06
Clothianidin	103.86	0.83	7.94	105.20	2.41	4.58
Imidacloprid	88.81	1	11.25	88.24	3.63	8.24
Thiacloprid	104.60	1.58	15.15	113.23	4.72	8.34
Thiamethoxam	99.61	1.21	12.20	108.42	4.35	8.03

3.3. LOD and LOQ values

The studies were performed in 10 replicates at a single concentration (10 µg L^{-1}) and the standard deviation (SD) and relative standard deviation (RSD%) values of each pesticide were calculated. The LOD value is determined as 3 times the calculated standard deviation values for each pesticide active ingredient. LOQ value was calculated as 10 times the standard deviation values calculated for each pesticide active ingredient (Table 7).

Çizelge 7. Ortalama, standart sapma, yüzde relatif standart sapma, LOD, LOQ ve MRL değerleri

Table 7. *Mean, SD, RSD%, LOD, LOQ and MRL values*

	Acetamiprid (µg kg^{-1})	**Clothianidin (µg kg^{-1})**	**Imidacloprid (µg kg^{-1})**	**Thiacloprid (µg kg^{-1})**	**Thiamethoxam (µg kg^{-1})**
Mean	11.47	10.20	8.92	11.68	8.57
SD	0.39	0.36	0.34	0.34	0.41
RSD%	0.03	0.04	0.04	0.03	0.05
LOD	1.18	1.09	1.03	1.03	1.22
LOQ	3.93	3.65	3.44	3.45	4.07
EU-MRL	200	40	500	500	200

Looking at similar studies, Özel and Tiryaki (2017) found that the average reuptake value of imidacloprid and dimethoate for both apple varieties (Golden Delicious and Starking Delicious) was 88.34% (RSD 7.72%), reuptake of the whole method was found as 89.50% (RSD 12.02%) by the researchers. Durmaz and Tiryaki (2018) determined that the uptake from Golden D was found as 8.36 to 14.03% with repeatability values between 70.87-112.99% (average reuptake 89.32%). The uptake for the Starking D apple sample, it was found between 69.08-100.3% with repeatability values of 1.96-12.88%. Aysal et al. (2007), Ramadan et al. (2015), Bayrak (2018) and Pietrzak et al. (2019) found the method validation parameters within the values specified in SANTE (2017). Suganthi and Bhuvaneswari (2018) conducted studies for the detection of neocitonoid residues in tomatoes in India. They performed calibration study in the range of 25-500 µg kg^{-1}. In addition to this, researchers have determined the recovery of imidacloprid less than the limits (70-120%) specified in SANTE (2017). In our research, calibration study was done in the range of 5-150 µg kg^{-1} in order to reach lower limits. At the same time imidacloprid and other neonicotinoids were recorded in accordance with SANTE (2017). LOD and LOQ values in our study were found to be lower compared to the above study.

4. Conclusions

In this study, QuEChERS method was used for the analysis of 5 neonicotinoid residues in a single injection in tomato samples. It was observed that chromatographic separation was ended 4.279 th. minutes and the peaks were separated without overlapping with each other. Also, the chromatographic separation was over in as little as 1 minute. However, the total analysis time was extended to 10 minutes for the column to be cleaned at high temperature. This method allows for simultaneous analysis of the active ingredients imidacloprid, acetamiprid, thiamethoxam, clothianidin and thiacloprid in tomato samples prepared with QuEChERS. Method validation parameters such as linearity, accuracy (recovery), precision (reproducibility and reproducibility), LOD and LOQ were examined and found to be within SANTE (2017) limits.

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