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Simple Method for Determination of Fungicides in Citrus Fruits by Liquid Chromatography–Tandem Mass Spectrometry

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Abstract A simple method for the determination of four fungicides (thiabendazole, imazalil, *o*-phenylphenol, and diphenyl) in citrus fruits has been developed. After spiking surrogates of these fungicides, the sample was extracted with acetonitrile, salted out, and the water was simultaneously removed using anhydrous magnesium sulfate and sodium chloride. The extract was first purified with a primary secondary amine and octadecylsilane, followed by the addition of dimethyl sulfoxide as a keeper solvent, and subsequently concentrated under a nitrogen stream. The compounds were analyzed by liquid chromatography–tandem mass spectrometry using the atmospheric pressure photoionization interface. The recoveries and relative standard deviations (RSDs) of the fungicides (1 mg kg^{-1}) were satisfactory (recovery 92–114 %; RSD <10 %). An evaluation with Shewhart QC plots revealed that all data points are within the controlled area, thus confirming the robustness of the method for analyzing the fungicide content of citrus fruits. The sample preparation time for ten samples was approximately 2 h, highlighting the time and labor efficiency of the method.

Keywords Fungicides · QuEChRES method · LC-MS/MS · Citrus fruits

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Introduction

Fungicides are used to prevent the growth of fungi on citrus fruits during storage or transportation. Four fungicides, i.e., thiabendazole (TBZ), imazalil (IMZ), *o*-phenylphenol (OPP), and diphenyl (DP), have been approved as food additives for citrus fruits that are imported to Japan. Fruits are examined for these fungicides at quarantine stations and institutes of public health. In Japan, the maximum residue limits (MRLs) for citrus fruits are 10 mg kg^{-1} for TBZ and OPP, 5 mg kg^{-1} for IMZ, and 70 mg kg^{-1} for DP, and these values are identical to those recommended by *Codex Alimentarius*, except for DP. Generally, IMZ and the other three fungicides (TBZ, OPP, and DP) are determined by two independent methods. In order to determine IMZ, the sample is typically extracted twice with ethyl acetate after the addition of anhydrous sodium sulfate, and then purified using a liquid-liquid extraction technique under pH-controlled conditions (Norman and Fouse 1978). The purified extract is concentrated and analyzed using a high-performance liquid chromatography (HPLC) system coupled to an ultraviolet (UV) detector. UV detection is less accurate because of matrix interference. For the determination of TBZ, OPP, and DP, the sample is typically extracted twice with ethyl acetate and then concentrated in vacuo. After the test solution is diluted with water, it is analyzed via HPLC using a fluorescence detector (Kitada et al. 1982). The preparation time for both methods is 15 h. Thus, determining the presence of the aforementioned fungicides in citrus fruits using the methods described is both laborious and time consuming. If a method capable of simultaneously determining all four fungicides is developed, the efficiency of quarantine examinations and auxiliary inspections at institutes of public health could be enhanced.

Previously, we have proposed methods for determining fungicides in citrus fruits via HPLC analysis using a

fluorescence detector (Akutsu et al. 1998; Kakimoto et al. 1997). Recently, Ito et al. developed a unique method to determine TBZ, IMZ, and OPP by infusing the samples into a tandem mass spectrometry (MS/MS) system, equipped with an electrospray-ionization (ESI) interface (Ito et al. 2003). However, they did not analyze DP as it is difficult to ionize owing to its nonpolar structure, unlike the other compounds that ionize readily via the ESI or atmospheric pressure chemical ionization (APCI) techniques. Recently, Yoshioka et al. introduced a method for the determination of TBZ, IMZ, R14821 [1-(2,4-dichlorophenyl)-2-(1*H*-imidazole-1-yl)-1-ethanol; a metabolite of IMZ], OPP, and DP using a liquid chromatography–mass spectrometry (LC–MS) system, equipped with an atmospheric pressure photoionization (APPI) interface (Yoshioka et al. 2004). The APPI interface can simultaneously ionize DP, TBZ, IMZ, and OPP via sample irradiation with high-energy UV light in the presence of a dopant (toluene). The clear advantage of this procedure is that it enables the detection of all four fungicides using only a single method. However, the preparation of the test solutions is complicated because sample pH has to be adjusted using sodium hydroxide and the solutions need to be purified via the double-extraction method.

With regard to sample preparation, multiresidue methods for the determination of pesticides in food are useful and methods for determining pesticide residues in agricultural products, including citrus fruits, are well established (Albero et al. 2004; Arenas et al. 1996; Luke et al. 1975; Luke et al. 1988). Anastassiades et al. previously introduced the QuEChERS method, a simple, rapid, and easy multiresidue method, for the detection of pesticides in food (Anastassiades et al. 2003). The characteristic steps involved in the QuEChERS method are as follows: (1) extraction with acetonitrile in a disposable tube, (2) one-step salting out and removal of water from acetonitrile using anhydrous magnesium sulfate ($MgSO_4$) and sodium chloride (NaCl), and (3) rapid purification, termed "dispersive solid-phase extraction (dispersive-SPE)," using a primary secondary amine (PSA). The merits of this method include a decreased cost of experimental apparatus and solvents, as well as a reduction in assay time, without the loss of analytical accuracy. In a follow-up study, Lehotay et al. demonstrated that by using a combination of gas chromatography–mass spectrometry and liquid chromatography–tandem mass spectrometry (LC–MS/MS), the QuEChERS method can be used to effectively monitor more than 200 pesticide residues (Lehotay et al. 2005a). Recently, we proposed the methods that utilize the QuEChERS method for pesticide analysis (Okihashi et al. 2005; Okihashi et al. 2007). In those previous studies, IMZ and TBZ were successfully determined using LC–MS/MS, operating using the ESI interface (Lehotay et al. 2005a). Even though we did not examine the applicability of the QuEChERS method for the analysis of OPP and DP, we considered the QuEChERS protocol a promising candidate for the sample preparation of OPP and DP.

Herein, we developed a simple method that combines the QuEChERS method and LC–MS/MS analysis (using the APPI interface) to determine the presence of four fungicides in citrus fruits. Furthermore, we also validated our method and reported the results obtained using this method.

Materials and Methods

Reagents and Standards

Acetonitrile, toluene, and acetone used for sample preparation were of pesticide analytical grade, $MgSO_4$ and NaCl were of analytical grade, acetonitrile used for LC was of LC-MS grade (Wako Pure Chemical, Osaka, Japan), and heptafluoro-n-butyric acid (HFBA) was of LC-MS grade (Tokyo Kasei Kogyo, Tokyo, Japan). The water used in the experiment was purified with a Milli-Q system (Millipore, Bedford, MA).

Dispersive PSA was obtained from Agilent Technologies (Santa Clara, CA, USA), octadecylsilane (ODS) was from Wako Pure Chemical, and dimethyl sulfoxide (DMSO; spectrophotometric grade) was from Sigma-Aldrich (St. Louis, MO, USA).

The standard solutions for TBZ, OPP, and DP were obtained from Wako Pure Chemical. TBZ-$^{13}C_6$ and IMZ-d_5 were purchased from Hayashi Pure Chemical (Osaka, Japan). The standard for IMZ was obtained from Dr. Ehrenstorfer (Augsburg, Germany), while OPP-$^{13}C_6$ and DP-d_{10} were purchased from Cambridge Isotope Laboratories (Andover, MA, USA). The stock solutions (1000 μg mL^{-1}) of each fungicide and their respective surrogates, except for OPP-$^{13}C_6$, were prepared in acetone and stored at 4 °C. The weight of the stock solutions in their respective containers (each a glass tube with a glass fitting and a label) was recorded at the start and the end of the experiments. To maintain an optimum concentration of the stock solution, the weight of acetone or acetonitrile lost during storage was calculated and the stock solutions were replenished accordingly before use. A surrogate mixture of TBZ-$^{13}C_6$, IMZ-d_5, and DP-d_{10} (100 μg mL^{-1}) as well as OPP-$^{13}C_6$ (10 μg mL^{-1}) was prepared in acetonitrile. All subsequent dilutions were made with acetonitrile.

Instruments and Conditions

An Agilent 1100 LC-MS/MS system consisting of a binary pump, an autosampler, and a tandem mass spectrometer (API-3000) equipped with an APPI ion source (AB SCIEX, Framingham, MA, USA) was used. The system was used in combination with an XTerra Phenyl analytical column (100 × 2.1 mm i.d., 3.5 μm, Waters, Milford, MA, USA).

A mobile phase consisting of acetonitrile and water (each containing 5 mM of HFBA) was used at a flow rate of 0.2 mL min^{-1}. During the gradient elution analysis, the initial concentration of the mobile phase was set at 25 % acetonitrile and this increased linearly to 50 % over a duration of 20 min. The column temperature was set at 40 °C.

The fungicides were all monitored using the positive mode. The mass spectrometer was operating at an ion source temperature of 400 °C and a capillary voltage of 1600 V. Toluene was infused as a dopant into the APPI interface at a flow rate of 20 μL min^{-1}. The multiple reaction monitoring (MRM) transitions were selected and optimized by testing each fungicide at a concentration of 1 μg mL^{-1} in a water-acetonitrile (1:1) system containing 5 mM of HFBA. The combinations of the precursor (Q1) and product ions (Q3), collision energy (CE), declustering potential (DecP), focusing potential (FP), retention time (RT), and limits of quantification (LOQ; signal/noise ratio >10) for the fungicides are listed in Table 1.

Samples

Three blank samples of citrus fruits (grapefruit, orange, and lemon) were obtained from a supermarket in Osaka, Japan. The homogenated citrus fruit mixture was dispensed into a clean polyethylene bag and kept at −20 °C until analysis.

Extraction and Cleanup Procedures

Chopped citrus fruits were homogenized for 3 min using a food processor. Next, 10 g of the homogenate was placed in a 50-mL disposable polypropylene (PP) tube and 0.1 mL of surrogate mixture was then added into the tube. Subsequently, 10 mL of acetonitrile was added and the tube was vigorously shaken for 1 min.

Thereafter, 4 g of $MgSO_4$ and 1 g of NaCl were added and the tube was vigorously shaken for another 1 min to aid the salting out process and to remove water from the acetonitrile phase. After centrifugation (1200 × *g*, 10 min), the supernatant was transferred to a new 15-mL PP tube containing 0.2 g of PSA, 1 g of ODS, and 1.2 g of $MgSO_4$, and the resultant suspension was vigorously shaken for 1 min. After centrifugation (1200×*g*, 10 min), an aliquot (1 mL) of the supernatant was transferred to a glass tube. The solution was concentrated under a nitrogen gas stream at 40 °C after the addition of 0.2 mL of DMSO as a keeper solvent. The concentrated extract was reconstituted with water containing 5 mM of HFBA and analyzed with LC–MS/MS. Figure 1 shows an outline of the method.

Recovery Tests

Recovery tests were conducted by fortifying each sample (grapefruit, orange, and lemon) with all four fungicides at a concentration of 1 mg kg^{-1}. After the fortified samples were incubated at room temperature for 30 min, the fungicides were extracted using the aforementioned procedures. The recovery tests were conducted five times.

Quality Control

The quality control (QC) material was prepared by fortifying 1 mg kg^{-1} of DP-pooled grapefruit samples. The concentrations of IMZ, TBZ, and OPP in the sample were previously determined at 1.37, 0.87, and 0.32 mg kg^{-1}, respectively. The sample was dispensed into a clean polyethylene bag and frozen at −20 °C until analysis. The fungicides in the samples ($n = 3$) were measured for eight consecutive days.

Results and Discussion

LC–MS/MS Conditions

In this study, HFBA, a volatile ion pair reagent, was added to the eluent. Typical chromatograms obtained during the analysis of the four fungicides without and with the addition of

Table 1 Mass spectrometric parameters for the determination of fungicides by LC–MS/MS

Compound	MS/MS transition, *m/z* Q1 > Q3	CE (eV)	DecP (V)	FP (V)	RT (min)	LOQ (μg mL^{-1})
TBZ	200 > 175	35	46	150	2.6	0.005
IMZ	297 > 159	29	41	150	10.8	0.005
OPP	170 > 141	35	36	140	12.0	0.05
DP	154 > 128	37	41	140	18.4	0.2
TBZ-$^{13}C_6$	208 > 181	35	51	180	2.5	–
IMZ-d_5	302 > 159	31	46	160	10.7	–
OPP-$^{13}C_6$	176 > 147	35	36	140	12.0	–
DP-d_{10}	164 > 136	164	46	150	18.1	–

CE collision energy, *DecP* declustering potential, *FP* focusing potential, *RT* retention time, *LOQ* limits of quantification

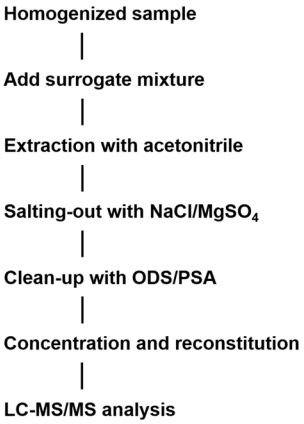

Fig. 1 Flow chart of the proposed method

HFBA are shown in Fig. 2a, b, respectively. The shapes of the TBZ and IMZ peaks and their separation improved after the addition of HFBA, thus enabling a more selective and sensitive analysis of the fungicides. For the simultaneous detection of all four fungicides, we adopted the APPI interface (in the positive mode) to promote the ionization of DP, a photoactivating compound with infused toluene as a dopant.

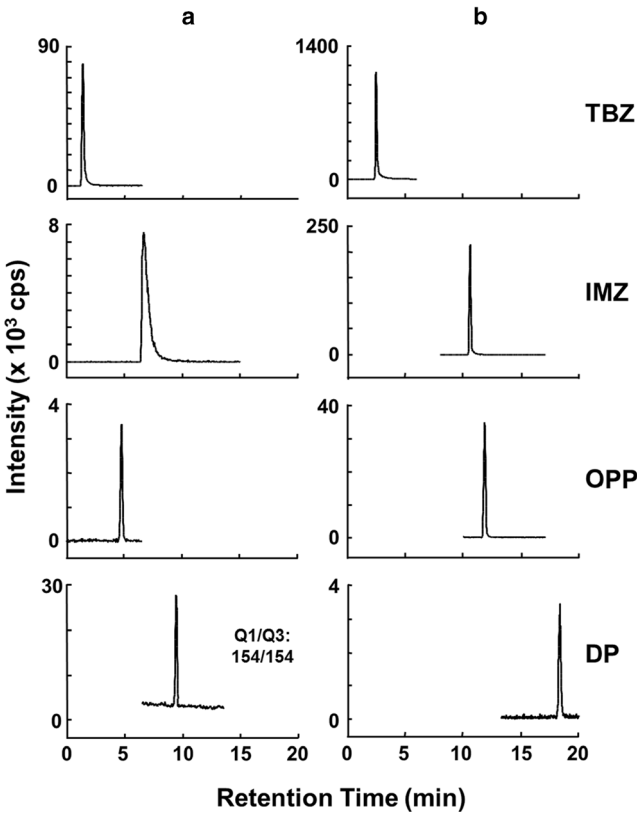

Fig. 2 Typical MRM chromatograms of fungicides (1 μg mL^{-1}) that were analyzed with (**b**) and without (**a**) an ion-pair reagent; injection volume 10 μL. Elution was performed a gradient mode with 1×10^{-3} % acetic acid (AcOH) in a water-acetonitrile system (A)

The infusion rate of the dopant was determined based on the infusion of the pesticide mixture in the eluent (which contains 50 % acetonitrile) into the MS/MS system. The peak areas of these fungicides plateaued when the dopant infusion rates between 15 and 25 μL min^{-1}; therefore, the infusion rate of toluene was set at 20 μL min^{-1}.

Calibration Curves

While testing the proposed method using surrogates, the peak-area ratios (the fungicides/their corresponding surrogates) of the calibration curves were plotted against the fungicide concentrations. Meanwhile, when testing the proposed method without using surrogates, the peak-areas of the fungicides were plotted against the fungicide concentrations to generate the calibration curves.

The calibration curves consisted of five points (0.2, 0.5, 1.0, 2.0, and 5.0 mg mL^{-1}). The standard solutions did not contain the matrix. The curves were linear in the range that extends from the LOQ of each species (Table 1) to 5 μg mL^{-1}. The slope, intercept, and r^2 of the mean linear regression equations obtained using five replicates are shown in Table 2.

Preparation of Test Solution

In order to optimize the method, we modified the QuEChERS method by (1) adding ODS in the purification step and (2) using DMSO as a keeper solvent in the concentration step.

After the extraction with acetonitrile and salting out, 8 mL of extract was obtained. The purification step in the original QuEChERS method involves a dispersive-SPE using either only PSA or both PSA and ODS (Anastassiades et al. 2003; Lehotay et al. 2005a). The test solution obtained using the original purification method separated into two phases, an oily phase derived from the citrus peel and an aqueous phase. The oily phase trapped DP, and thus affected DP detection, giving only 30 % of DP recovery. The use of PSA in combination with ODS is one of the useful steps utilized during the cleanup of fatty foods (Gillespie et al. 1995; Lehotay et al. 2005b). ODS was added during the purification step to remove the oily phase. Satisfactory recovery levels of DP (>95 %) were observed after adding over 1 g of ODS per 8 mL of the acetonitrile extract. After the dispersive cleanup of the 8 mL extract with both PSA and ODS, the volume of the supernatant was reduced to 6 mL.

During the concentration phase, DMSO was added as a keeper solvent to prevent the loss of DP, which is a volatile compound. Approximately 80 % of the total DP was lost during the concentration phase without the addition of DMSO. A blank matrix extract that was fortified with the fungicides was analyzed with 0, 0.05, 0.1, 0.2, and 0.4 mL

Table 2 The parameters of calibration curves (a) with and (b) without surrogates

Compound	Equation	Slope	Intercept	r^2
TBZ[a]	$y = 1.13x + 0.144$	1.13 ± 0.013	0.144 ± 0.016	0.998
IMZ[a]	$y = 1.16x - 0.007$	1.16 ± 0.011	-0.007 ± 0.022	1.000
OPP[a]	$y = 15.5x - 0.486$	15.5 ± 0.977	-0.486 ± 0.425	0.999
DP[a]	$y = 1.62x - 0.142$	1.62 ± 0.134	0.142 ± 0.094	0.998
TBZ[b]	$y = 8.84 \times 10^6 x + 52{,}927$	$8.84 \times 10^6 \pm 1.62 \times 10^6$	$52{,}927 \pm 3.52 \times 10^5$	0.999
IMZ[b]	$y = 1.91 \times 10^6 x - 23{,}613$	$1.91 \times 10^6 \pm 2.78 \times 10^5$	$-23613 \pm 8.55 \times 10^4$	0.999
OPP[b]	$y = 3.03 \times 10^5 x + 5343$	$3.03 \times 10^5 \pm 9.04 \times 10^4$	5343 ± 4367	0.999
DP[b]	$y = 3.22 \times 10^4 x + 245$	$3.22 \times 10^4 \pm 1853$	245 ± 1853	0.998

y peak-area ratio, x concentration of fungicides (μg mL^{-1})

of DMSO. Adding over 0.2 mL of DMSO to 1 mL of the purified extract prevented the loss of DP. The optimal volume of DMSO, at which its effect on chromatograms is minimal, was 0.2 mL.

We compared the time required to prepare the test solutions of ten citrus fruit samples using this method against those of two other conventional methods (Kitada et al. 1982; Norman and Fouse 1978). The former was about 2 h, while the latter was 15 h. In our method, the centrifugation time could be further shortened to 5 min under the same conditions without causing a decay of precipitant. Thus, the developed method is easier to use than conventional methods.

Recovery Tests

Figure 2 shows typical chromatograms of citrus fruits that were fortified with fungicides at the concentration of 1 mg kg^{-1}. By applying the surrogate correction, all the recoveries and relative standard deviations (RSDs) were observed at satisfactory levels. The recoveries with surrogate correction and RSDs were 92–114 and <10 %, respectively (Table 3 (A)). Even without using the surrogates, the recovery and RSD were at acceptable levels (recovery: 75–129%; RSD: < 25%) (Table 3 (B)). With the exception of TBZ and DP in grapefruits, the "raw" recoveries of fungicides (*i.e.*, those obtained without applying the surrogate correction) obtained using this method were practically within 70–120% (RSD, < 20%). Thus, the values were within the acceptable recovery levels for the development of multi-residue methods to analyze pesticides in agricultural products. The recoveries (and RSDs) of TBZ and DP were 129% (3.3%) and 96% (23%), respectively. As such, this method can be used to screen fungicides in citrus fruits without using any surrogates.

By omitting the use of surrogates, the procedure can be further shortened. The concentration step that includes adding

Table 3 Recoveries and RSDs of fungicides from citrus fruits samples (A) corrected by surrogates and (B) without correction by surrogates

Compound	Recovery (RSD) (%)					
	Grapefruit		Orange		Lemon	
	A	B	A	B	A	B
TBZ	101 (2.5)	129 (3.3)	103 (5.2)	106 (3.9)	101 (0.7)	92 (3.5)
IMZ	95 (1.6)	102 (6.7)	103 (5.2)	83 (4.0)	95 (0.6)	85 (5.4)
OPP	108 (4.2)	91 (1.6)	111 (3.3)	90 (2.1)	114 (4.2)	75 (4.5)
DP	95 (8.0)	96 (23)	92 (4.5)	91 (7.7)	105 (3.3)	97 (6.5)

Fortified levels, 1 mg kg^{-1} ($n = 5$)

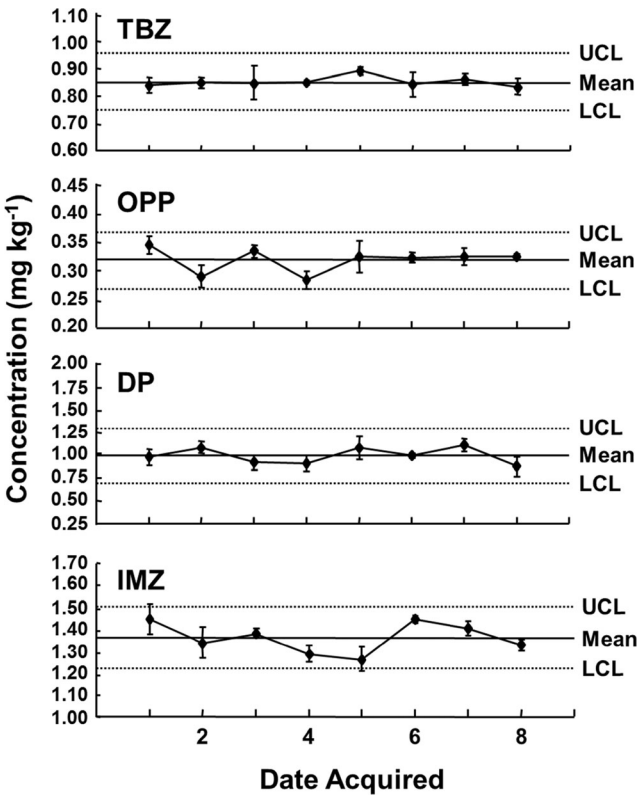

Fig. 3 The QC plots (<UCL>LCL) for TBZ, OPP, DP, and IMZ concentrations in citrus samples. Analysis of fungicides ($n = 3$) for eight consecutive days. TBZ 0.96–0.77 μg mL^{-1}; OPP 0.37–0.27 μg mL^{-1}; DP 1.29–0.70 μg mL^{-1}; IMZ 1.51–1.23 μg mL^{-1}

Table 4 Determination of fungicides in commercially available citrus fruits

Sample	Mean concentration (range; number of detected samples) (mg kg^{-1})				
		TBZ	IMZ	OPP	DP
Grapefruit	($n = 20$)	ND (0.3–0.6; 2)	0.4 (0.3–3.6; 18)	ND	ND
Orange	($n = 6$)	ND (0.2–1.4; 3)	0.6 (1.2–4.3; 5)	ND	ND
Lemon	($n = 4$)	0.6 (0.8–1.5; 3)	0.6 (1.1–1.7; 3)	ND (0.3; 1)	ND

ND, <0.2 mg kg^{-1}

DMSO to the extract (a step that requires 10 min per sample) compensates for the loss of the surrogates in the test solution. After undergoing dispersive-SPE, the concentration of the extract was 1 g mL^{-1}. To avoid potential problems that could occur during chromatographic analysis (*i.e.*, caused by injecting the acetonitrile solution), the extract should be diluted with an aqueous solution, such as the mobile phase used in this study, to give a 25% acetonitrile solution. Without the concentration step, the concentration of the test solution was 0.25 g mL^{-1}. The concentrations (in μg mL^{-1}) of the surrogates were as follows: IMZ-d_5, 0.25; TBZ-$^{13}C_6$, 0.25; OPP-$^{13}C_6$, 0.025; and DP-d_{10}, 0.25. OPP-$^{13}C_6$ cannot be quantified using the proposed method because its LOQ is 0.050 μg mL^{-1}. If the surrogates are not used, the concentration step can be omitted. In procedures that do not include the concentration step, the LOQs (in μg mL^{-1}) of the fungicides would be as follows: IMZ, 0.02; TBZ, 0.02; OPP, 0.2; and DP, 0.8. No obvious differences in the results of the recovery tests were observed (data not shown).

Quality Control

The QC materials were analyzed for eight consecutive days, and the data were evaluated using a Shewhart QC plot (Fig. 3). Each central line represents the aggregate average measurement. The upper control limit (UCL) and lower control limit (LCL) were calculated using the three sigma method. The points and bars represent the means of three separate experiments and their standard deviations. All data points are within the controlled area, hence confirming that this is a robust method for the determination of fungicides in citrus fruits.

Monitoring Fungicides in Citrus Fruits

The proposed method was used to determine the levels of fungicides in thirty citrus samples, which were obtained from markets in Osaka. The results are summarized in Table 4. OPP, TBZ, and IMZ were detected in 1, 8, and 26 samples, respectively. However, DP was not detected in any of the samples. The concentrations of all three fungicides detected were lower than their corresponding MRLs.

Conclusions

We have developed a simple method for the determination of fungicides in citrus fruits utilizing the QuEChERS method and LC–MS/MS. The proposed method can detect all tested fungicides reliably and precisely. Thus, this method can be used to monitor the presence of fungicides in citrus fruits.

Compliance with Ethical Standards

Conflict of Interest The authors declare that there are no conflicts of interest regarding the publication of this paper.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed Consent Not applicable.

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