



Trace Enantioselective Determination of Imidazolinone Herbicides in Various Food Matrices Using a Modified QuEChERS Method and Ultra-Performance Liquid Chromatography/Tandem Mass Spectrometry

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Received: 21 January 2019 / Accepted: 17 July 2019 / Published online: 13 August 2019
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Abstract

A modified QuEChERS method was developed for simultaneous enantioselective determination of three imidazolinone herbicides (imazethapyr, imazamox, and imazapic) in two oil crops (soybeans and peanuts) and three food crops (wheat, maize, and rice) by chiral reversed-phase ultra-performance liquid chromatography/tandem mass spectrometry. Sample extraction was performed with 20 mL of methanol adjusted to pH 4 with 1% aqueous acetic acid. The supernatant was then cleaned with a primary secondary amine and graphitized carbon black. Several significant factors affecting the performance of the method were optimized. Under the optimum conditions, good linearity ($R^2 \geq 0.9931$) and acceptable recoveries (63.5–111.5%, relative standard deviation $\leq 22.7\%$) were obtained for each enantiomer. The limits of detection and quantification ranged from 0.34 to 1.5 $\mu\text{g}/\text{kg}$ and 1.1 to 5.0 $\mu\text{g}/\text{kg}$, respectively. For all three imidazolinone herbicides, the *S*-enantiomers eluted before the *R*-enantiomers. Finally, several food samples (soybeans, peanuts, wheat, maize, or rice) were analyzed by this method. The enantiomers of the three imidazolinone pesticides (imazethapyr, imazamox, and imazapic) were not found in these samples at the microgram per kilogram level.

Keywords Imidazolinone herbicide · Enantioselective quantification · QuEChERS pretreatment · UPLC–MS/MS

Introduction

More than 30% of pesticides, and more than 40% of those sold in China, are chiral pesticides (Garrison 2011; Sekhon 2009; Zhou et al. 2009a). Because organisms can recognize enantiomers and bind them at different sites, the metabolism, bioactivity, degradation behavior, and impact on target and non-target organisms of a pesticide differ when exposed to chiral environments (Garrison et al. 2011; Gamiz et al. 2016; Zhao et al. 2018). Racemic pesticides show poor efficiency, with at least 50% of the pesticide going on to pollute the environment and even harm non-target organisms (Armstrong et al. 1993; Lewis et al. 1999; Perez-Fernandez et al. 2011). However, most chiral pesticides are sold as racemates (Garrison 2006)

and deemed to be one compound by traditional analysis, which means that their enantioselectivity is often neglected (Elmarakby et al. 2001; Li et al. 2012). Therefore, analysis of pesticide enantiomers is critical to provide more accurate data to assess food safety and environmental risks.

Imazapic [(*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methylnicotinic acid], imazethapyr [(*RS*)-5-ethyl-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-nicotinic acid], and imazamox [(*RS*)-2-(4-isopropyl-4-methyl-5-oxo-2-imidazolin-2-yl)-5-methoxymethylnicotinic acid] belong to a class of imidazolinone (IM) herbicides. All of the three imidazolinone herbicides have a chiral center (Fig. 1) and inhibit acetolactate synthase (ALS). A lack of this enzyme affects the synthesis of branched amino acids, resulting in a weed-control effect (Beckie et al. 2012). In a previous study, a Chiralcel OJ column was successfully used to separate enantiomers of five IM herbicides (Lao and Gan 2006). In a further study of the elution order of IM enantiomers, the *S*-enantiomer of each chiral IM eluted before the *R*-enantiomer (Lao and Gan 2007;

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Fig. 1 The chemical structures of chiral imidazolinone herbicides (*chiral center)

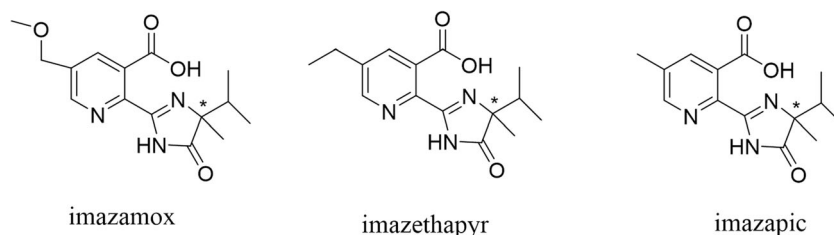


Table 1 Optimized MRM conditions for analysis of imidazolinone herbicides by UPLC–MS/MS

Compound	Chemical constitution	Ion source	Precursor ion	Quantification ion	Confirmation ion	Fragmentor (v)
Imazamox	C ₁₅ H ₁₉ N ₃ O ₄	ESI+	306.1	261.1 (20)	192.99 (22)	120
Imazethapyr	C ₁₅ H ₁₉ N ₃ O ₃	ESI+	290.1	245 (16)	177 (24)	80
Imazapic	C ₁₄ H ₁₇ N ₃ O ₃	ESI+	276.1	231 (18)	162.9 (22)	80

Qian et al. 2009; Zhou et al. 2010). Studies of the enantioselective toxicities of IM herbicides in maize, rice, *Arabidopsis thaliana*, and Michigan Cancer Foundation-7 cells showed that the *R*-enantiomers were more toxic than the *S*-enantiomers (Hsiao et al. 2014; Qian et al. 2009; Wei et al. 2016; Xie et al. 2017; Zhou et al. 2009b, 2010).

IM pesticides are highly effective broad-spectrum herbicides that are mainly used to control weeds in soybeans, peanuts, rice, and other field crops (Grichar 2002; Sudianto et al. 2013; Stout et al. 1996). Considering that these pesticides have potentially harmful effects on the environment and pose health risks to humans, many countries have established maximum residue levels for IM herbicides in crops. These standards include the European Community Regulation No. 396/2005 (EC 2005) and China National Standard No. GB 2763-2016. Studies on IM herbicide residues have mainly concentrated on soil and water (Bzour et al. 2019; Kemmerich et al. 2015; Safarpour et al. 2004). Simultaneous enantioselective analytical methods for IM herbicides in multiple food matrices are rare. Therefore, to protect public health and control food quality, it is of great significance to establish a rapid and reliable method for IM herbicide enantiomers in food matrices.

The QuEChERS method was first proposed in 2003 (Anastassiades et al. 2003), and a modified version has been increasingly applied to the extraction of various compounds with good results (Da Silva et al. 2018; Farajia et al. 2018; Farajzadeh et al. 2018; He et al. 2017; Huang et al. 2018; Jiang et al. 2018). Ultra-performance liquid chromatography/tandem mass spectrometry (UPLC–MS/MS) can be used for accurate and effective trace analysis of many pesticides in complex matrices (Deng et al. 2018; Magiera et al. 2016; Tan et al. 2018; Tang et al. 2013). The QuEChERS method

has been combined with UPLC–MS/MS for multiresidue detection of pesticides.

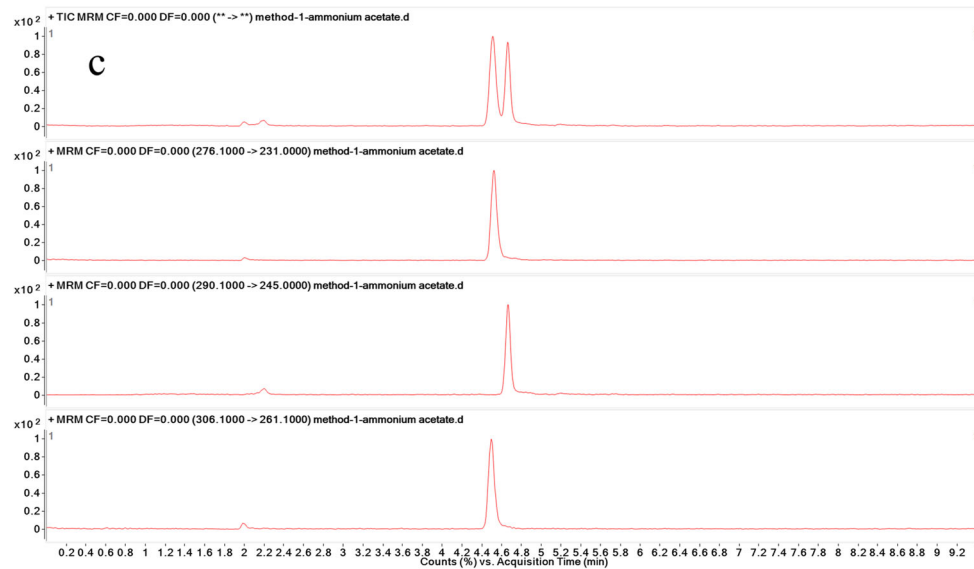
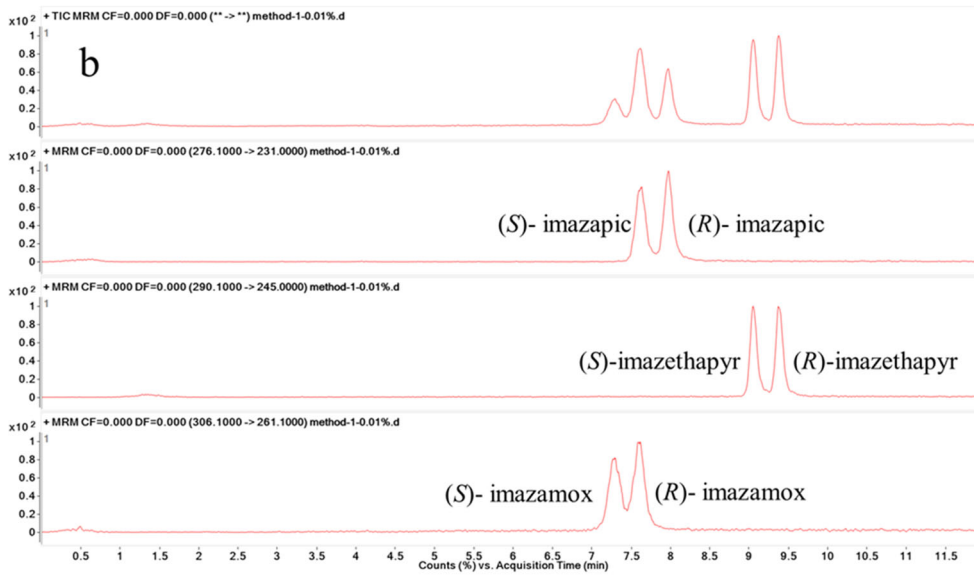
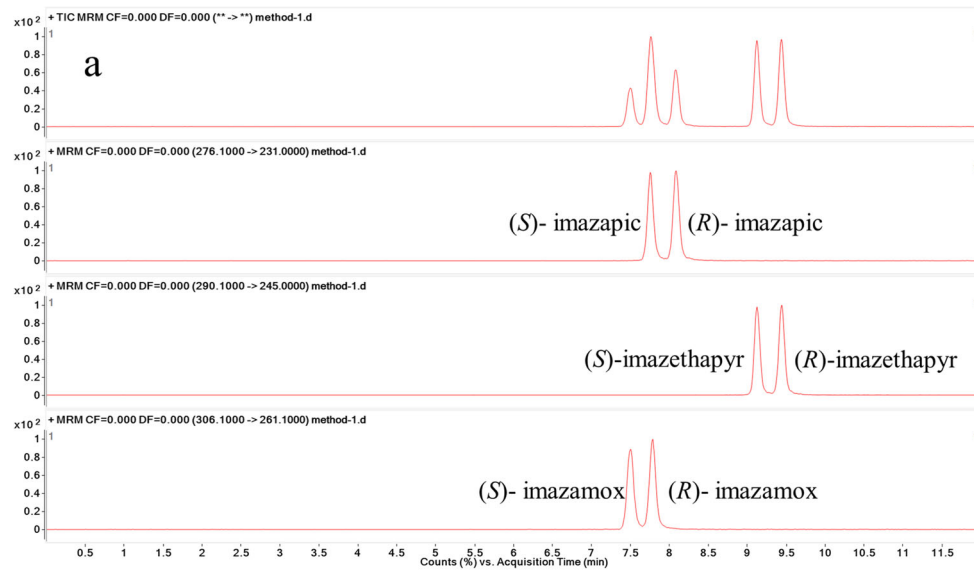
Herein, an effective and reliable chiral analytical method was developed to determine IM herbicide enantiomers in food matrices (soybeans, peanuts, maize, rice, and wheat) using UPLC–MS/MS with a Chiralcel OJ-3R column. Chiral separation parameters, including the mobile phase type and ratio, were systematically evaluated. Different extractants and pH values were compared, and the purification effects of different sorbents were evaluated. To the best of our knowledge, this is the first report of simultaneous enantioselective analysis of imazethapyr, imazamox, and imazapic in the above food matrices. The results will facilitate more accurate assessment of the risks posed by these compounds to human health and the environment.

Materials and Methods

Chemicals and Reagents

Racemic imazethapyr (99.0% purity), imazamox (98.8% purity), and imazapic (98.5% purity) were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). Six enantiomers (98% purity) were prepared at the Institute of Pesticides and Environmental Toxicology, Guangxi University (Guangxi, China). The enantiomeric excess of each enantiomer was greater than 98%. HPLC-grade acetonitrile (ACN) and formic acid were purchased from Merck (Darmstadt, Germany). Analytical grade methanol,

Fig. 2 Compared HPLC chromatograms of imidazolinone herbicides on the Chiralcel OJ-3R and the same elution procedure under different mobile phase conditions. (a) 0.1% formic acid aqueous solution/acetonitrile; (b) 0.01% formic acid aqueous solution/acetonitrile; (c) 5 mmol ammonium acetate aqueous solution/ acetonitrile)



glacial acetic acid, and sodium chloride were purchased from Chengdu Kelong Chemical Reagent Factory (Chengdu, China). Purified water was obtained using a Milli-Q treatment system (Millipore, Billerica, MA, USA). The sorbents, including primary secondary amine (PSA), graphitized carbon black (GCB), and octadecylsilane (C18), were purchased from Agilent Technologies (Santa Clara, CA, USA).

Standard stock solutions (1000 mg/L) of racemic imazethapyr, imazamox, and imazapic were prepared in HPLC-grade ACN. Standard working solutions of imazethapyr, imazamox, and imazapic with concentrations of 5, 50, 100, 500, and 1000 µg/L containing both enantiomers at 2.5, 25, 50, 250, and 500 µg/L concentrations, respectively, were prepared from the stock solutions by serial dilution. Matrix-matched standard solutions were prepared at the same concentrations by adding blank soybean, peanut, maize, wheat, or rice sample extracts. All solutions were stored in the dark at $-20\text{ }^{\circ}\text{C}$ until required for analysis. No degradation was observed for 3 months.

Instrumentation

Chromatography analysis was performed on an Agilent 1290 Series Rapid Resolution UPLC System. Simultaneous enantioseparation of the IM herbicides was performed using a Chiralcel OJ-3R column (150 mm \times 4.6 mm i.d., 3-µm particle size; Daicel, Tokyo, Japan) after injection of 2 µL of the standard working solution. Chiral analysis was conducted with solvent A (0.1% formic acid aqueous solution) and solvent B (HPLC-grade ACN) using a gradient program (0 min, 80% A; 2 min, 75% A; 4 min, 65% A; 6 min, 55% A; 8 min, 65% A; and 11 min, 80% A). The mobile phase flow rate was maintained at 0.4 mL min^{-1} , and the column was kept at $30\text{ }^{\circ}\text{C}$.

An Agilent 6460 Triple Quadrupole LC–MS/MS spectrometer operated in positive electrospray ionization mode was used to quantify the IM herbicides. MS analyses were performed in multiple reaction monitoring mode. Of the two product ions, that with the highest sensitivity was taken as the quantitative ion and that with the second highest sensitivity was used as the qualitative ion. The standard pesticide solution prepared with ACN was injected into the mass spectrometer to optimize the MS instrument parameters. The optimized multiple reaction monitoring protocol for data collection is shown in Table 1.

Sample Preparation Procedure

Samples of soybeans, peanuts, wheat, maize, and rice were obtained from a local supermarket in Nanning (China). Each sample was homogenized before storage at $-20\text{ }^{\circ}\text{C}$.

For each food sample, 5 g was placed in a 50-mL Teflon centrifuge tube and an aliquot of standard solution at the

Fig. 3 Compared HPLC chromatograms of imidazolinone herbicides on the same Chiralcel OJ-3R column and mobile phase (A: 0.1% formic acid aqueous solution; B: acetonitrile) under different elution procedures conditions (a 0 min, 80% A/20% B; 2 min, 75% A/25% B; 4 min, 65% A/35% B; 6 min, 55% A/45% B; 8 min, 65% A/35% B; and 11 min, 80% A/20% B; b 0 min, 75% A/25% B; 2 min, 65% A/35% B; 5 min, 60% A/40% B; 7 min, 70% A/30% B; and 9 min, 75% A/25% B; c 0 min, 65% A/35% B; 2 min, 60% A/40% B; 4 min, 50% A/50% B; 6 min, 25% A/75% B; 7 min, 50% A/50% B; 10 min, 65% A/35% B; d 0 min, 50% A/50% B; 1 min, 40% A/60% B; 2 min, 30% A/70% B; 4 min, 20% A/80% B; 5 min, 40% A/60% B; 6 min, 50% A/50% B; e 0–12 min, 75% A/25% B)

required concentration was added. The samples were vortexed vigorously for 5 min to ensure that the standard solutions were dispersed evenly in the food matrices, and then allowed to stand at room temperature for 1 h. Methanol (20 mL) adjusted to pH 4 with 1% aqueous acetic acid was added, and the mixture was vortexed for another 5 min to fully extract the IM herbicides. Next, sodium chloride (4 g) was added, and the mixture was vortexed for 1 min and centrifuged for 5 min at 4100 rpm. The supernatant (2 mL) was collected from each sample and added to a 4-mL centrifuge tube containing PSA (50 mg) and GCB (30 mg). After centrifuging for 5 min at 5000 rpm, the supernatant was removed and filtered through a 0.22-µm nylon syringe filter.

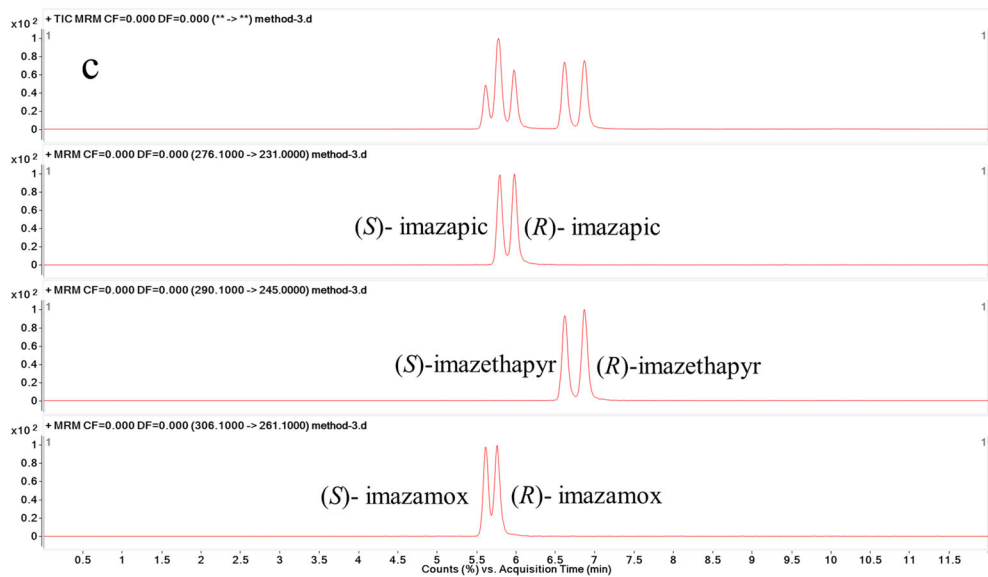
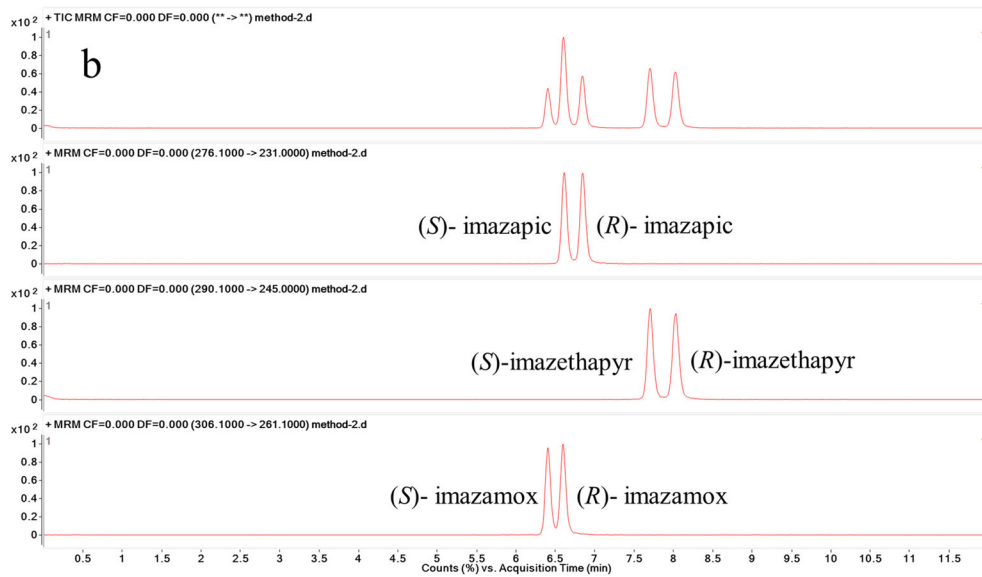
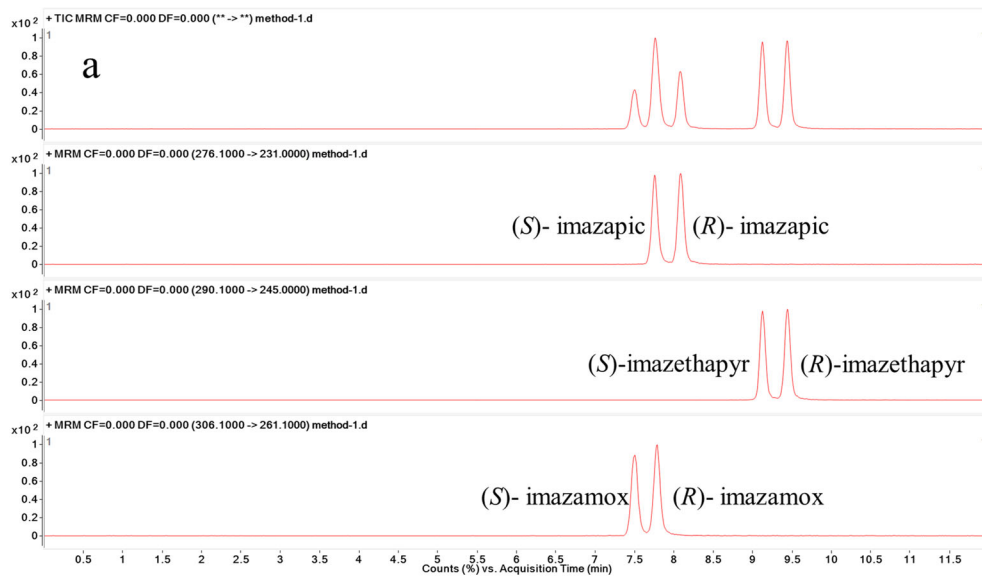
Method Validation

The specificity, linearity, limit of detection (LOD), limit of quantification (LOQ), matrix effect, accuracy, and precision were validated to evaluate the method performance.

Blank samples (soybeans, peanuts, wheat, maize, and rice) were analyzed to verify the absence of interfering species close to the retention times of the analytes. Linear regression analysis of the standard and matrix-matched solutions was performed to measure the linearity and is expressed as the correlation coefficient R^2 . The slope ratios of matrix-matched and pure solvent calibration curves were calculated to estimate the matrix-induced signal suppression/enhancement.

The LOD and LOQ corresponded to signal-to-noise ratios (S/N) of 3 and 10, respectively. The repeatability and reproducibility were determined by analyzing five replicates of each spiked sample (soybeans, peanuts, maize, wheat, and rice) at three different levels (2.5–50 µg/kg) on the same day and three nonconsecutive days, respectively. The accuracy was calculated from average recoveries, and the precision was analyzed using the intra- and interday relative standard deviations (RSD).

The stabilities of imazethapyr, imazamox, and imazapic in the solvent and matrices were investigated once per month.



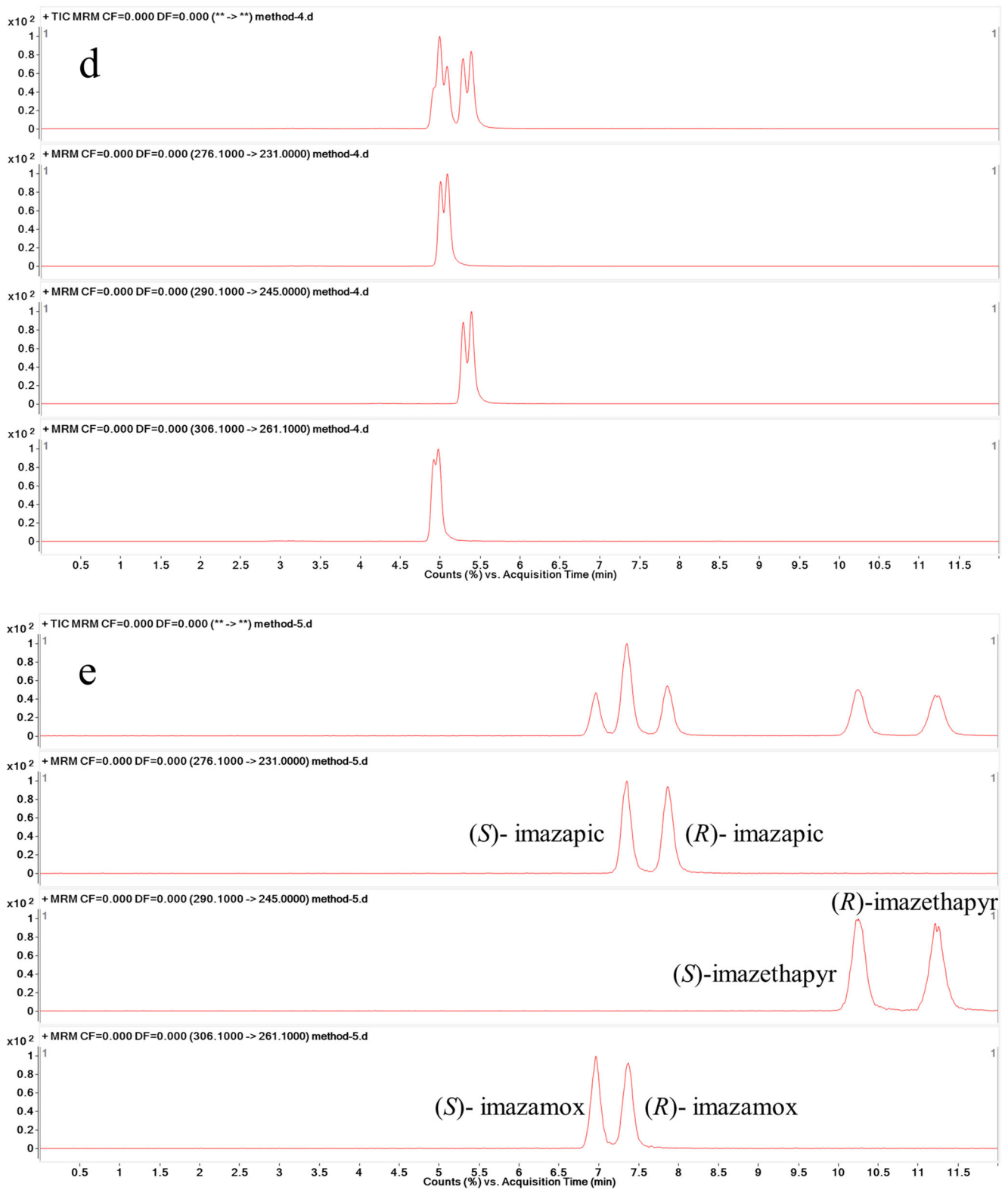
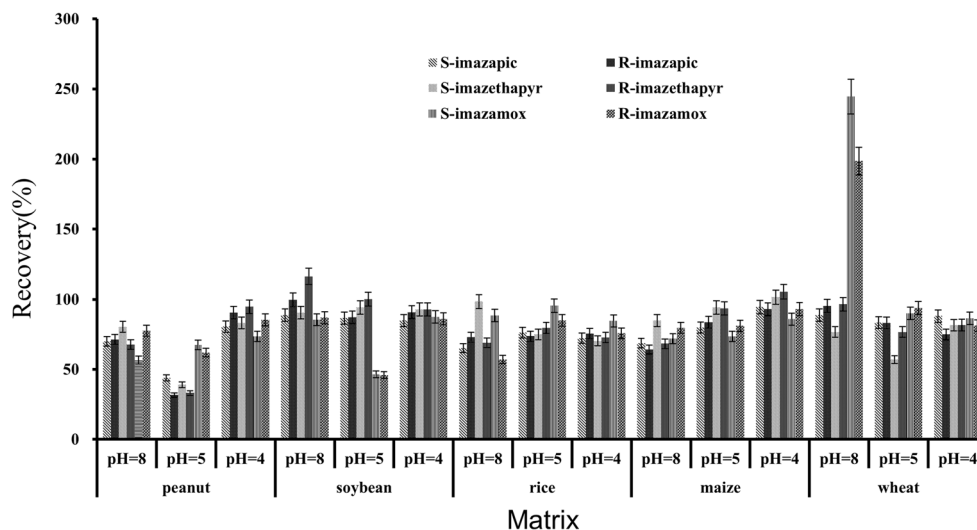


Fig. 3 (continued)

Fig. 4 Effect of methanol containing ammonium hydroxid, methanol containing 1% acetic acid aqueous solution (pH = 5) and methanol containing 1% acetic acid aqueous solution (pH = 4) as extraction solvents for the targeted compounds in five matrix at the $10 \mu\text{g kg}^{-1}$ level for each enantiomer ($n = 5$)



Results and Discussion

Chromatographic Performance

The retention behavior, elution, and separation of chiral analytes are influenced by the mobile phase composition (Dousa et al. 2013). As imazethapyr, imazamox, and imazapic are pH-sensitive acidic herbicides, mobile phases with different pH values, including 0.01% formic acid aqueous solution/ACN, 0.1% formic acid aqueous solution/ACN, and 5 mmol ammonium acetate aqueous solution/ACN, were compared to study the effect on IM herbicide enantioseparation. The separation results are shown in Fig. 2. The separation of *S*- and *R*-enantiomers failed when 5 mmol ammonium acetate aqueous solution/ACN was used, and neither enantiomer could be accurately determined for enantioselective analysis. The mobile phase of 0.1% formic acid aqueous solution/ACN performed better than 0.01% formic acid aqueous solution/ACN in terms of response values and peak shape. This might be attributed to 0.1% formic acid providing abundant H^+ ions and preventing acid dissociation in the acidic herbicides, which would improve the chromatographic peak shapes (Sack et al. 2015). Therefore, a mixture of 0.1% formic acid aqueous solution (solvent A)/ACN (solvent B) was selected as the mobile phase.

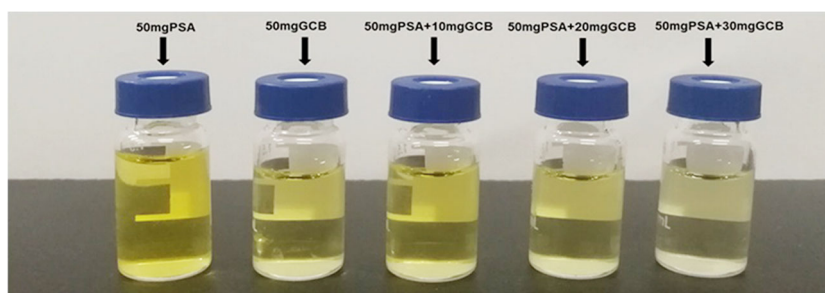
To obtain the best peak shapes and retention behavior, the following elution procedures, including gradient elution and

isocratic elution, were tested: (i) 0 min, 80% A/20% B; 2 min, 75% A/25% B; 4 min, 65% A/35% B; 6 min, 55% A/45% B; 8 min, 65% A/35% B; and 11 min, 80% A/20% B; (ii) 0 min, 75% A/25% B; 2 min, 65% A/35% B; 5 min, 60% A/40% B; 7 min, 70% A/30% B; and 9 min, 75% A/25% B; (iii) 0 min, 65% A/35% B; 2 min, 60% A/40% B; 4 min, 50% A/50% B; 6 min, 25% A/75% B; 7 min, 50% A/50% B; and 10 min, 65% A/35% B; (iv) 0 min, 50% A/50% B; 1 min, 40% A/60% B; 2 min, 30% A/70% B; 4 min, 20% A/80% B; 5 min, 40% A/60% B; and 6 min, 50% A/50% B; (v) 0–12 min, 75% A/25% B. Gradient elution procedures (iii) and (iv) failed to successfully separate the enantiomers (Fig. 3). Although gradient elution procedure (ii) had the shortest elution time among the five programs and showed good baseline separation for imazethapyr and imazamox, it failed to achieve good baseline separation of imazapic. However, gradient elution procedure afforded (i) better peak shapes, a shorter elution time, and higher responses than the isocratic elution procedure (v). Gradient elution procedure (i) also fully eluted all six enantiomers in less than 10 min. Consequently, procedure (i) was selected for use in this study.

Mass Spectrometry Optimization

To obtain higher precursor ion signal intensities and optimize the fragmentation patterns, positive and negative ion modes

Fig. 5 Effect of different sorbents for imidazolinone herbicides and purification performances in maize matrix at the $25 \mu\text{g kg}^{-1}$ level for each enantiomer



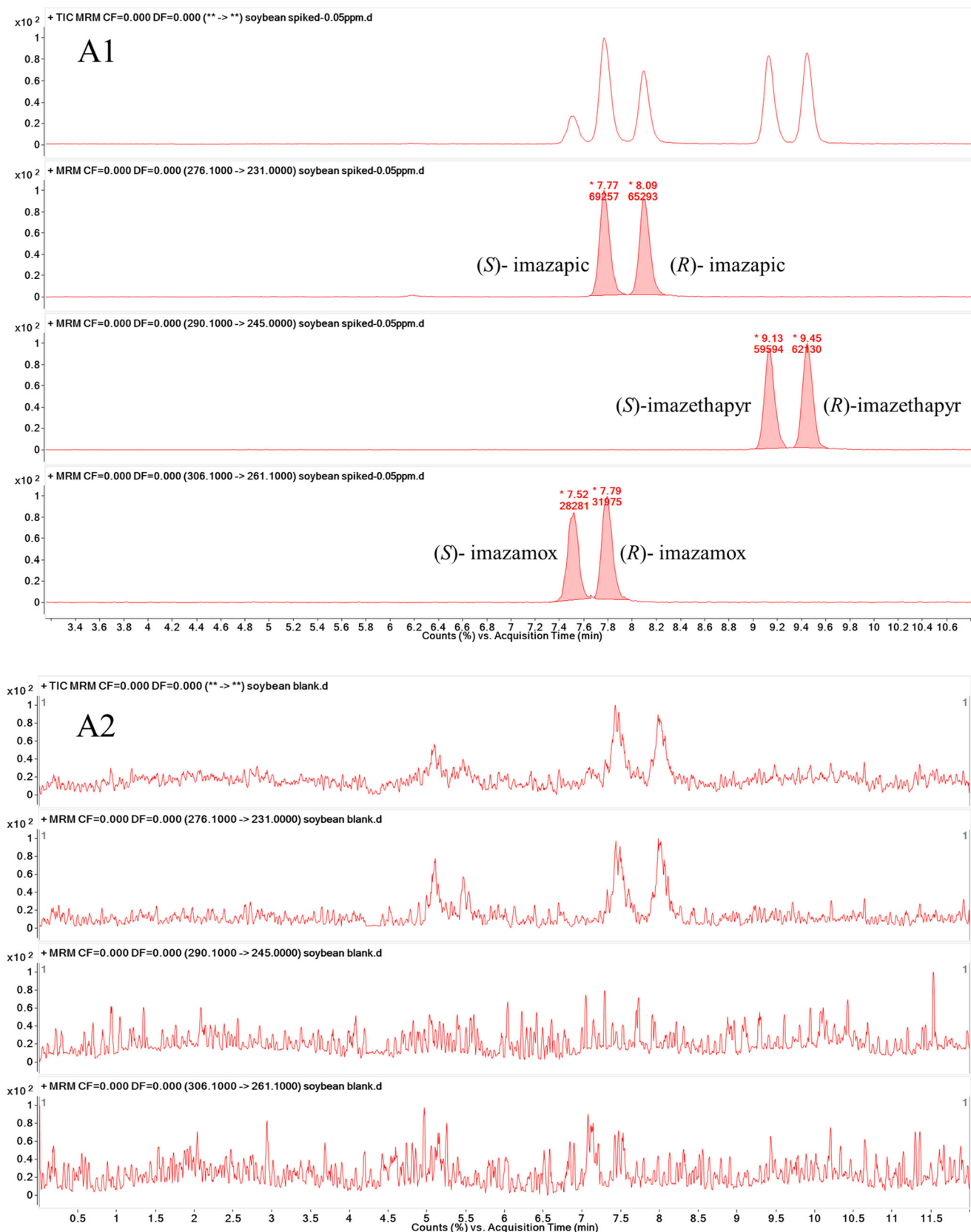


Fig. 6 Typical UPLC-MS/MS chromatograms of the various blanks and spiked samples. **A1** soybeans spiked, **A2** soybeans blank, **B1** peanuts spiked, **B2** peanuts blank, **C1** wheat spiked, **C2** wheat blank, **D1** maize spiked, **D2** maize blank, **E1** maize spiked, **E2** maize blank. The spiking level was $25 \mu\text{g kg}^{-1}$ for each enantiomer

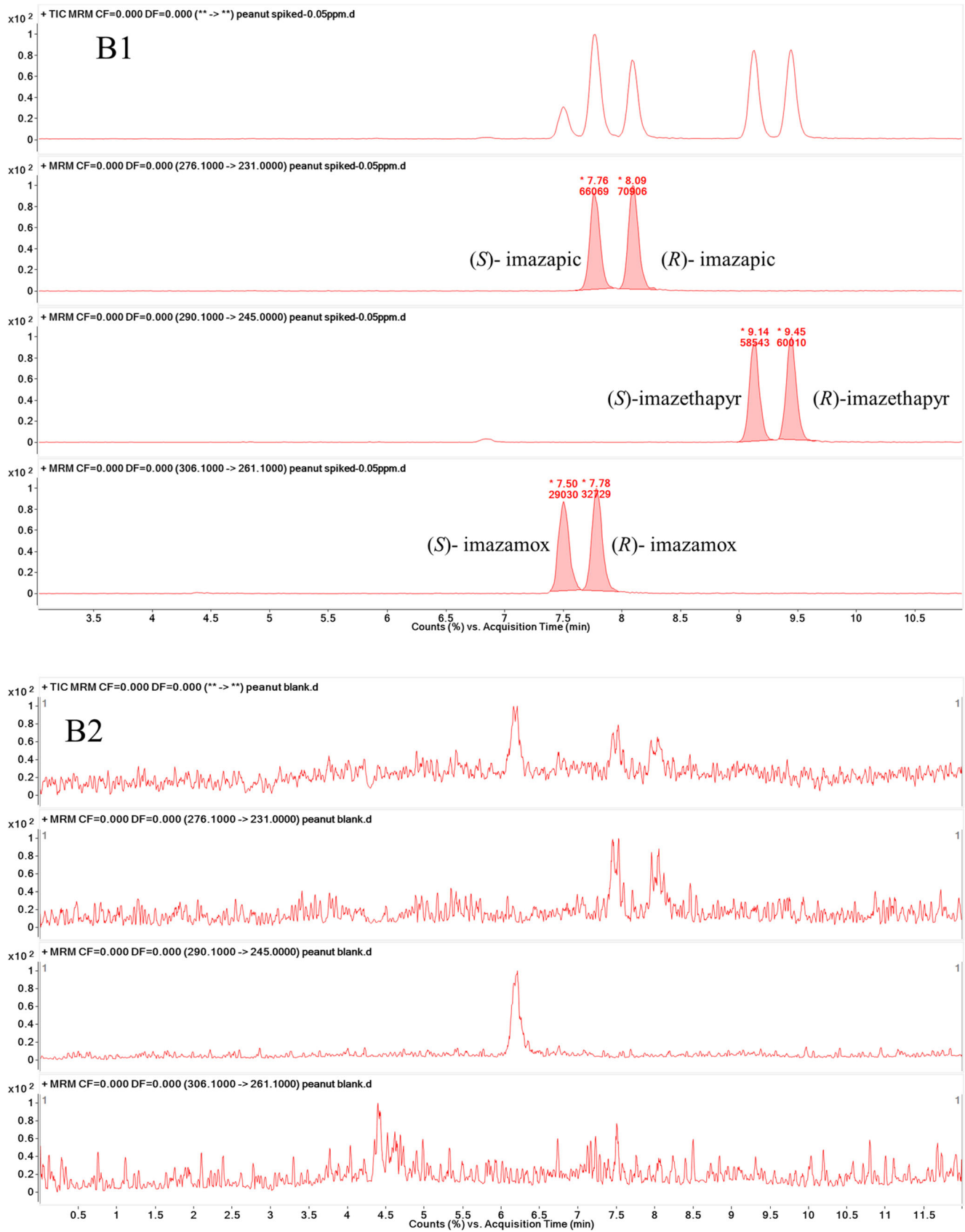


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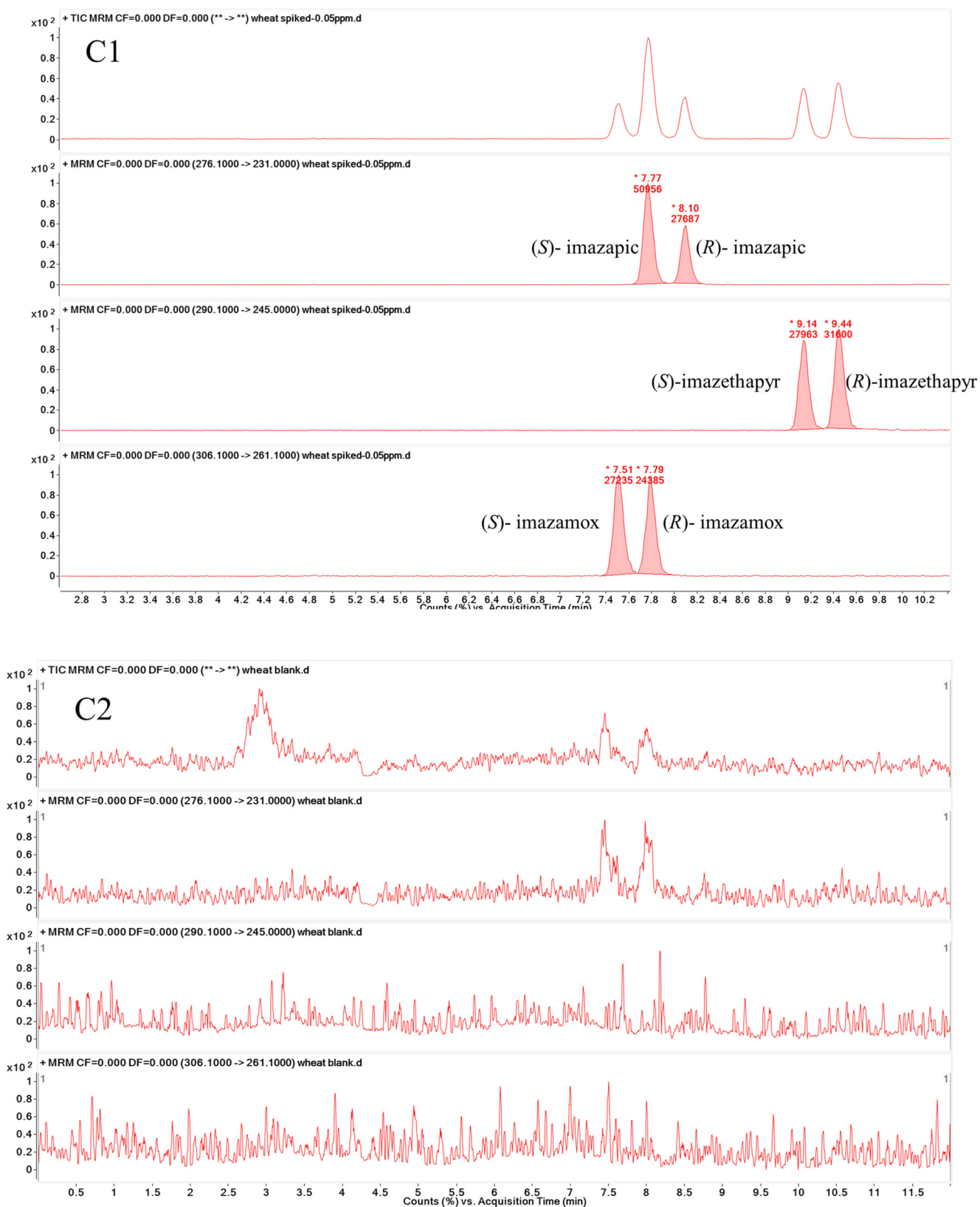


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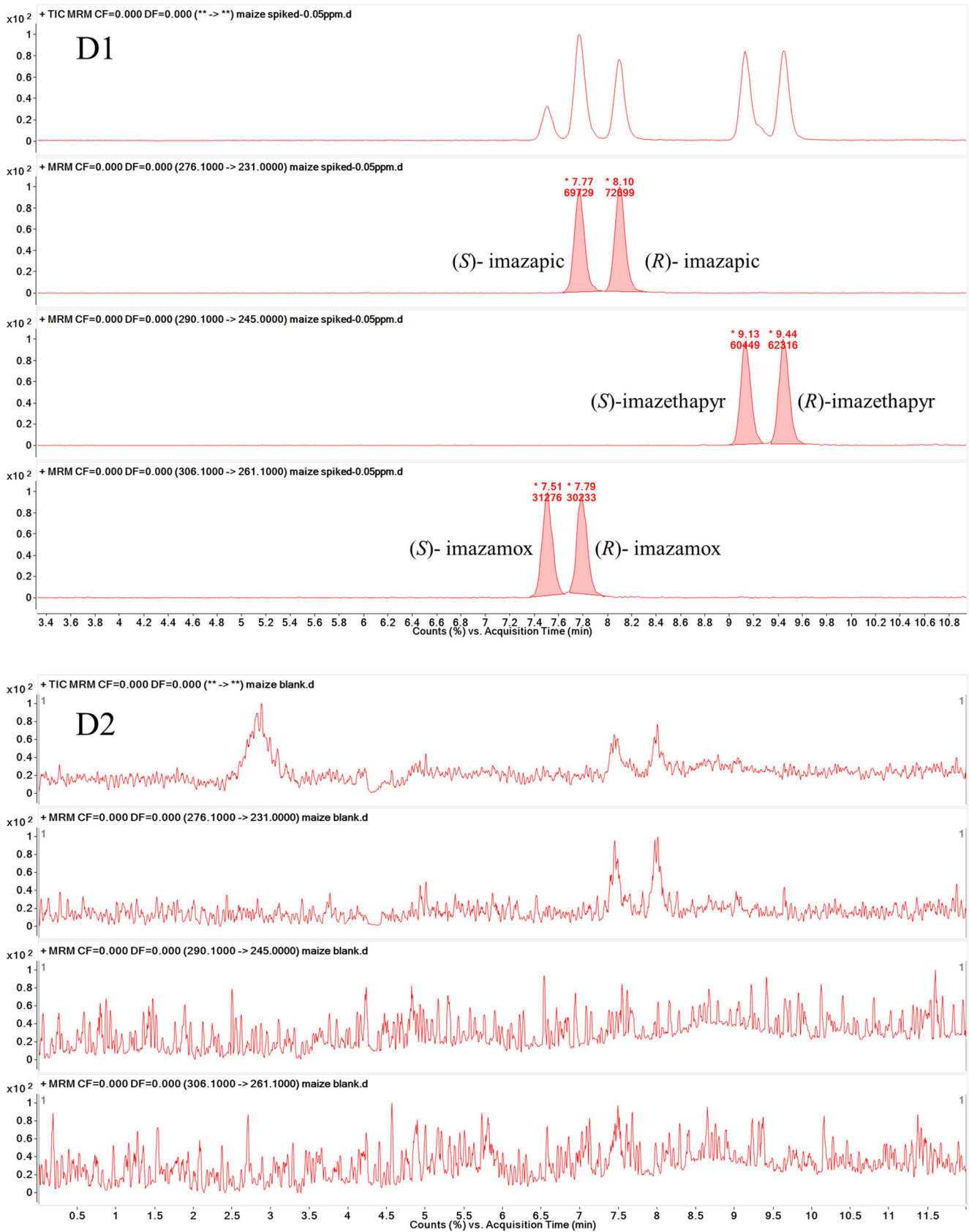


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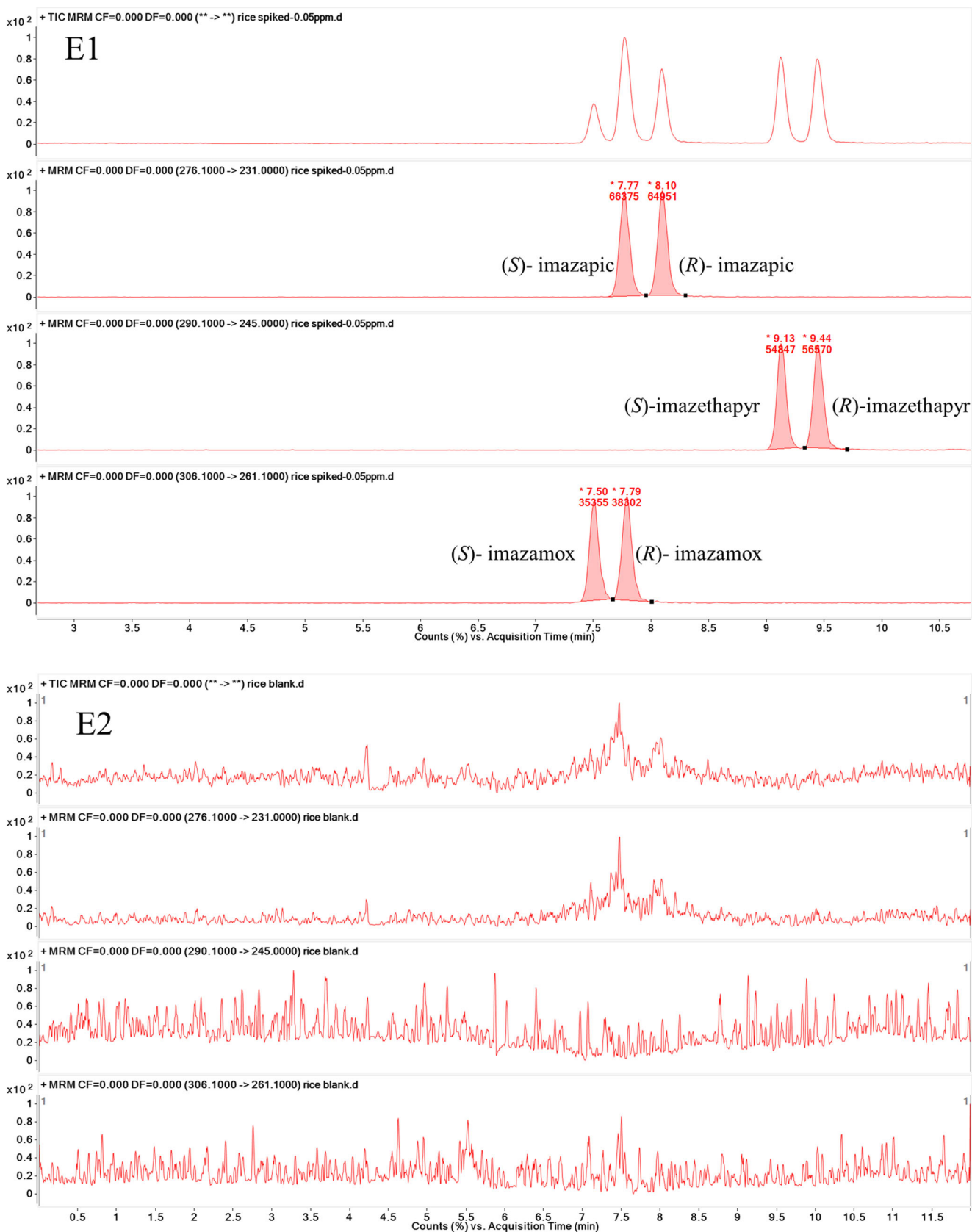


Fig. 6 (continued)

Table 2 Comparison of the slopes of the calibration curves and calculation of signal suppression/enhancement (SSE) in solvent and in matrices, LODs, and LOQs for the imidazolinone herbicides

Enantiomer	Matrix	Regression equation	R^2	SSE	LOD ($\mu\text{g}/\text{kg}$)	LOQ ($\mu\text{g}/\text{kg}$)
<i>S</i> -imazapic	Solvent	$y = 1,099,779x - 15,468$	1	–	–	–
	Peanut	$y = 1,226,664x - 10,438$	1	1.115	0.41	1.4
	Soybean	$y = 1,219,850x - 19,533$	1	1.109	0.47	1.6
	Rice	$y = 1,246,168x - 20,142$	1	1.133	0.48	1.6
	Maize	$y = 1,268,500x - 20,930$	0.9985	1.153	0.41	1.4
	Wheat	$y = 1,195,570x - 25,106$	0.9968	1.087	0.35	1.2
<i>R</i> -imazapic	Solvent	$y = 1,148,436x - 17,659$	1	–	–	–
	Peanut	$y = 1,226,664x - 10,438$	1	1.068	0.38	1.3
	Soybean	$y = 1,209,928x - 18,990$	1	1.054	0.38	1.3
	Rice	$y = 1,419,223x - 35,551$	0.9931	1.236	0.49	1.7
	Maize	$y = 1,306,071x - 20,936$	0.9986	1.137	0.36	1.2
	Wheat	$y = 847,932x - 18,036$	0.9963	0.738	0.72	2.4
<i>S</i> -imazethapyr	Solvent	$y = 901,194x - 12,507$	0.9988	–	–	–
	Peanut	$y = 977,480x - 8531$	0.9995	1.085	0.45	1.5
	Soybean	$y = 962,645x - 13,410$	0.9975	1.068	0.40	1.3
	Rice	$y = 998,328x - 14,919$	0.9986	1.108	0.54	1.8
	Maize	$y = 1,019,957x - 15,014$	0.9989	1.132	0.51	1.7
	Wheat	$y = 675,431x - 12,717$	0.9959	0.749	0.88	2.9
<i>R</i> -imazethapyr	Solvent	$y = 938,397x - 13,693$	0.9989	–	–	–
	Peanut	$y = 1,025,693x - 10,741$	1	1.093	0.44	1.5
	Soybean	$y = 1,005,815x - 13,164$	1	1.072	0.34	1.1
	Rice	$y = 1,025,667x - 16,035$	1	1.093	0.53	1.8
	Maize	$y = 1,068,966x - 27,217$	0.9966	1.139	0.55	1.8
	Wheat	$y = 827,513x - 16,110$	0.9965	0.882	0.75	2.5
<i>S</i> -imazamox	Solvent	$y = 424,826x - 6388.4$	0.9966	–	–	–
	Peanut	$y = 490,764x - 3331.5$	0.9996	1.155	1.0	3.4
	Soybean	$y = 457,329x - 8182.9$	0.9969	1.077	1.3	4.3
	Rice	$y = 491,339x - 7588.4$	0.9974	1.157	1.5	4.9
	Maize	$y = 493,332x - 8167.3$	0.9977	1.161	1.2	4.0
	Wheat	$y = 474,668x - 9669.2$	0.9957	1.117	1.5	5.0
<i>R</i> -imazamox	Solvent	$y = 428,468x - 4849$	0.9986	–	–	–
	Peanut	$y = 502,826x - 2814.6$	0.9997	1.174	0.98	3.3
	Soybean	$y = 485,243x - 5843.6$	0.9978	1.133	0.98	3.3
	Rice	$y = 503,261x - 8045.8$	0.9974	1.175	1.1	3.5
	Maize	$y = 505,213x - 7476.9$	0.9983	1.179	1.4	4.5
	Wheat	$y = 481,613x - 5660.5$	0.9994	1.124	1.2	3.9

SSE slope matrix-matched calibration/slope standard calibration in solvent

were compared. Positive electrospray ionization with an $[M+H]^+$ ion was ultimately selected to analyze the three IM herbicides. This result was attributed to all the IM compounds containing nitrogen, which stabilizes positive ions (Sack et al. 2015). The compounds were efficiently ionized under electrospray conditions (Martins et al. 2015), and the most abundant fragment ions were selected as quantitative and qualitative ions at the optimum collision voltage. The optimized precursor ions, product ions, fragmentor, and collision voltages are shown in Table 1.

Determination of the Elution Order for IM Herbicide Enantiomers

The enantiomers of imazamox, imazethapyr, and imazapic were obtained from the Institute of Pesticides and Environmental Toxicology, Guangxi University, using a Chiralcel OJ column and mobile phase of *n*-hexane/ethanol/acetic acid. An established method was used for enantiomer separation (Xie et al. 2017) with the same Chiralcel OJ column and mobile phase of *n*-hexane/ethanol/acetic acid. The

Table 3 Recoveries ($n = 15$, percent), RSD_P , and RSD_R for target compound from different matrices at three spiked levels, $RSDr$ intraday, which is the relative standard deviation for repeatability ($n = 5$); RSD_R inter-day, which is the relative standard deviation for reproducibility ($n = 15$)

Stereoisomer	Matrix	Spiked level ($\mu\text{g}/\text{kg}$)	Intraday ($n = 5$)						Inter-day ($n = 15$)	
			Day 1		Day 2		Day 3		Average recoveries (%)	RSD_R (%)
			Average recoveries (%)	$RSDr$ (%)	Average recoveries (%)	$RSDr$ (%)	Average recoveries (%)	$RSDr$ (%)		
<i>S</i> -imazapic	Peanut	2.5	81.5	7.7	79.1	11.6	82.4	6.2	81.0	8.6
		25	77.0	2.0	83.3	15.9	79.4	2.8	79.9	10.3
		50	106.2	1.1	104.7	2.0	105.8	2.0	105.6	1.7
	Soybean	2.5	65.2	7.5	64.5	5.9	66.9	4.5	65.5	5.8
		25	73.5	2.1	73.9	1.6	74.0	3.1	73.8	2.2
		50	84.0	0.9	83.4	2.2	83.5	1.4	83.6	1.5
	Rice	2.5	101.8	5.2	97.2	4.4	102.1	3.6	100.8	4.9
		25	85.1	3.3	86.1	3.6	90.0	2.8	87.1	4.1
		50	84.2	1.4	82.9	1.8	81.4	2.8	82.8	2.4
	Maize	2.5	102.4	5.5	102.0	8.9	101.4	3.9	101.9	6.0
		25	94.8	1.0	91.0	8.4	95.0	1.3	93.6	4.9
		50	96.0	1.8	96.1	2.3	96.0	2.8	96.0	2.2
	Wheat	2.5	105.7	11.3	97.2	4.4	107.2	8.3	106.0	8.7
		25	90.4	4.4	91.7	3.1	86.7	3.6	89.6	4.3
		50	92.4	3.5	95.2	1.4	95.1	1.4	94.2	2.5
<i>R</i> -imazapic	Peanut	2.5	76.5	7.0	80.1	12.7	84.8	4.5	80.5	9.3
		25	79.0	3.1	84.7	16.4	80.1	4.0	81.3	10.2
		50	105.5	2.4	105.5	2.4	104.6	1.1	105.2	2.0
	Soybean	2.5	70.3	5.7	67.9	11.8	72.7	5.9	70.3	8.1
		25	73.8	3.8	73.3	1.4	74.1	3.6	73.7	3.0
		50	82.6	1.9	83.1	4.4	82.2	2.1	82.6	2.9
	Rice	2.5	96.9	6.7	102.5	6.2	111.5	9.5	105.0	8.5
		25	85.6	2.0	86.4	3.7	88.3	2.3	86.8	2.7
		50	86.4	2.8	86.0	2.5	86.5	2.9	86.3	2.6
	Maize	2.5	92.1	10.9	98.3	10.0	95.8	5.3	95.4	8.8
		25	93.3	2.1	91.1	10.7	96.1	2.9	93.5	6.3
		50	94.8	2.3	92.6	3.0	95.9	3.6	94.4	3.1
	Wheat	2.5	78.5	15.2	75.9	5.7	82.0	10.7	78.8	11.0
		25	80.5	2.6	78.7	7.8	78.7	2.9	79.3	4.7
		50	93.6	2.9	87.2	4.2	91.5	7.3	90.8	5.7
<i>S</i> -imazethapyr	Peanut	2.5	83.3	8.3	81.6	10.7	88.9	8.6	84.6	9.6
		25	83.3	7.0	91.4	14.5	84.4	5.0	86.4	9.6
		50	106.5	1.7	104.4	2.8	104.3	2.4	105.1	2.3
	Soybean	2.5	90.9	8.0	82.9	16.5	92.7	2.8	88.9	10.7
		25	91.4	7.5	95.1	7.9	94.2	5.6	93.6	6.8
		50	91.0	1.6	92.2	1.8	88.8	2.4	90.7	2.4
	Rice	2.5	81.0	7.3	90.5	11.7	89.4	6.5	88.8	8.4
		25	82.1	8.6	79.6	2.6	87.5	14.6	83.1	10.7
		50	80.6	4.3	87.3	10.0	77.5	3.9	81.8	8.3
	Maize	2.5	81.3	7.3	85.6	9.5	84.1	5.5	83.7	7.4
		25	101.1	3.6	97.5	4.0	101.3	1.3	100.0	3.5
		50	103.7	4.5	103.4	2.1	101.5	3.4	102.9	3.4
	Wheat	2.5	63.6	9.9	63.5	4.2	65.7	3.0	64.2	6.1
		25	85.1	6.0	84.0	3.6	81.4	4.4	83.5	4.9
		50	79.9	2.6	81.9	5.0	80.1	4.8	80.6	4.1
<i>R</i> -imazethapyr	Peanut	2.5	87.4	7.4	81.1	15.8	91.6	7.8	86.7	11.3
		25	87.2	8.0	90.6	10.6	86.7	4.7	88.2	9.1
		50	105.3	1.9	106.1	2.4	102.8	1.6	104.7	2.3
	Soybean	2.5	91.6	6.9	84.8	13.3	94.8	2.2	90.4	9.1
		25	94.0	8.6	97.9	9.3	100.8	5.0	97.6	7.8
		50	90.5	1.8	92.2	1.8	89.7	0.7	90.8	1.8
	Rice	2.5	78.2	6.6	87.1	7.9	80.5	3.4	82.7	7.1
		25	82.8	10.5	79.0	3.0	90.3	16.7	84.0	13.0
		50	81.9	4.5	87.8	7.4	82.7	3.3	84.1	6.0
	Maize	2.5	78.8	12.6	84.3	10.6	88.4	4.9	83.8	10.2
		25	102.7	2.1	99.2	3.3	101.7	1.8	101.2	2.7
		50	103.3	2.2	101.9	5.8	105.0	3.1	103.4	3.9
	Wheat	2.5	92.1	13.3	96.7	5.8	104.4	9.0	97.8	10.5
		25	87.0	4.1	86.5	8.2	83.7	4.0	85.7	5.6

Table 3 (continued)

Stereoisomer	Matrix	Spiked level ($\mu\text{g}/\text{kg}$)	Intraday ($n = 5$)						Inter-day ($n = 15$)	
			Day 1		Day 2		Day 3		Average recoveries (%)	RSD _R (%)
			Average recoveries (%)	RSD _r (%)	Average recoveries (%)	RSD _r (%)	Average recoveries (%)	RSD _r (%)		
<i>S</i> -imazamox	Peanut	50	84.9	1.8	85.0	3.7	85.1	3.2	85.0	2.8
		2.5	74.2	14.3	73.4	14.9	71.3	5.1	73.0	12.2
		25	75.7	1.4	82.0	11.1	81.8	4.7	79.9	8.9
	Soybean	50	107.4	0.7	103.7	2.0	107.9	1.6	106.4	2.2
		2.5	103.8	12.0	108.6	10.8	98.3	15.2	103.5	12.5
		25	96.3	4.0	96.3	3.7	99.1	5.7	97.2	4.5
	Rice	50	96.1	2.1	97.5	5.4	96.3	1.6	96.6	3.3
		2.5	92.7	18.3	83.2	16.7	77.1	21.4	82.8	18.3
		25	84.0	13.4	82.6	7.3	88.4	12.2	85.0	11.0
	Maize	50	87.6	3.0	89.6	4.3	85.3	5.4	87.5	4.5
		2.5	104.8	4.1	97.3	8.7	105.6	4.6	102.6	6.7
		25	98.3	7.9	97.8	14.4	104.7	5.1	100.2	9.6
	Wheat	50	97.2	5.2	94.4	6.0	99.2	5.9	97.0	5.7
		2.5	96.2	18.2	93.9	14.7	74.0	6.9	88.0	18.2
		25	92.5	6.1	91.4	4.4	90.8	3.9	91.6	4.6
<i>R</i> -imazamox	Peanut	50	96.3	4.0	94.1	4.2	94.2	3.1	94.8	3.7
		2.5	69.2	7.9	71.9	14.7	67.7	3.6	69.6	9.9
		25	78.5	2.6	83.5	15.4	78.9	8.1	80.3	10.1
	Soybean	50	103.9	2.8	103.8	1.7	104.9	1.9	104.2	2.1
		2.5	85.6	15.9	89.3	14.0	84.2	6.5	86.4	12.2
		25	95.6	2.0	93.5	3.9	93.7	5.0	94.3	3.7
	Rice	50	99.0	2.1	102.6	4.7	103.1	3.3	101.6	3.8
		2.5	94.5	10.6	94.7	10.2	102.0	14.9	99.1	11.8
		25	84.8	15.0	80.8	4.0	88.4	11.3	84.7	11.5
	Maize	50	87.0	1.9	88.7	4.9	84.9	4.3	86.9	4.1
		2.5	79.5	13.8	73.6	13.4	86.9	15.1	80.0	14.9
		25	98.5	9.4	97.9	16.4	103.3	4.2	99.9	10.5
	Wheat	50	95.3	4.3	93.0	4.0	97.7	2.0	95.3	3.9
		2.5	93.1	13.4	88.3	22.7	108.2	5.9	96.6	16.3
		25	90.3	4.7	90.5	5.4	92.7	5.5	91.2	5.0
		50	100.3	2.8	99.7	4.1	98.7	2.0	99.6	2.9

previous study showed that the *S*-enantiomer eluted before the *R*-enantiomer for each enantiomer pair. In this study, standard solutions were prepared of the obtained enantiomers for instrumental analysis. The elution order of the enantiomers was determined from the enantiomer retention times. For each pair of enantiomers, the *S*-enantiomer eluted faster than the *R*-enantiomer.

Sample Preparation

For better extraction and purification, the traditional QuEChERS method was modified in this study. IM herbicides are amphoteric and can exist in three forms (anionic, neutral, or cationic) depending on the pH. Therefore, the influence of pH must be taken into account for efficient extraction. In this study, extractants with different pH values were compared. Acetic acid aqueous solution (1%) and ammonium hydroxide were added to methanol to adjust the pH. Extraction solutions with pH values of 4, 5, and 8 were tested (Fig. 4). When the

extractant was methanol containing ammonium hydroxide (pH 8), the recoveries of the different herbicides ranged from 57 to 245%. Methanol containing 1% aqueous acetic acid (pH 5) gave recoveries in the range 39–100%. Satisfactory recoveries were achieved for all food matrices when methanol containing 1% aqueous acetic acid (pH 4) was used for the extraction. Using the pH 4 extractant, all enantiomers of imazapic, imazethapyr, and imazamox would be deprotonated and easy to extract. Therefore, methanol containing 1% aqueous acetic acid (pH 4) was selected as the extractant.

Meanwhile, numerous sorbents were tested to remove impurities and improve the purification. Test A was performed using PSA (50 mg), test B using C18 (50 mg), test C using PSA (50 mg) and GCB (10 mg), test D using PSA (50 mg) and GCB (20 mg), and test E using PSA (50 mg) and GCB (30 mg). Satisfactory recoveries were obtained with all adsorbents, but their purification effects differed. For example, for the maize matrix, test E made the color clearer than any other sorbent (Fig. 5).

Considering both the recovery and purification effect, the PSA (50 mg) and GCB (30 mg) combination was selected as the sorbent.

Method Validation

Specificity, Linearity, LOD, and LOQ

The proposed method was applied to blank samples of different food matrices to evaluate the specificity of the method. No interference was detected at the retention times of the target analytes (Fig. 6). The linearity was determined using calibration curves prepared for acetonitrile, soybeans, peanuts, maize, wheat, and rice, and satisfactory linearity was observed ($R^2 \geq 0.9931$). The lowest point of the chromatogram used in the matrix-matched calibration was used to assess the S/N ratio (Mostafa et al. 2009). The LOD (three times the S/N ratio) range was 0.34–1.5 $\mu\text{g}/\text{kg}$, and the LOQ (ten times the S/N ratio) range was 1.1–5.0 $\mu\text{g}/\text{kg}$ (Table 2).

Matrix Effect

Suppression or enhancement of the analyte response is usually caused by codissolution of target compounds and other compounds and is referred to as the matrix effect. The slope ratios of the standards dissolved in sample matrices and those dissolved in the solvent were compared to verify whether matrix effects occurred. A slope ratio of less than -10% (0.912) is considered matrix suppression, and a ratio of more than 10% (1.065) is considered matrix enhancement (Zhu et al. 2013). The matrix effects of all enantiomers in the five matrices were evaluated, and matrix enhancement was observed for most enantiomers of imazethapyr, imazamox, and imazapic in the five matrices, with slope ratios in the range of 1.068–1.179 (Table 2). However, matrix suppression was also detected for *R*-imazapic, *S*-imazethapyr, and *R*-imazethapyr in wheat, with slope ratios of 0.738, 0.749, and 0.882, respectively. No matrix effect was observed for *R*-imazapic in soybeans. Matrix effects are usually caused by insufficient removal of endogenous compounds, such as fatty acids, phospholipids, pigments, and sugars, from the sample extracts (Matuszewski et al. 2003). To eliminate matrix effects and obtain more accurate data, all six stereoisomers were calibrated using external matrix-matching criteria.

Accuracy and Precision

The RSD (%), which incorporates repeatability and reproducibility, was used to assess the method precision, and the recoveries (%) of spiked samples were used to evaluate the accuracy. The repeatability and reproducibility were measured by comparing the standard deviations of the recovery percentages of spiked samples analyzed on the same day (intraday) and three different

days (interday), respectively. Three concentrations of each matrix were tested with each concentration of the five samples. All RSD values were less than 22.7% at the three fortified concentration levels (Table 3). The intraday and interday recovery ranges were 64.2–107.5% and 65.5–106% for *S*-imazapic, 67.9–111.5% and 70.3–105.2% for *R*-imazapic, 63.5–106.5% and 64.2–105.1% for *S*-imazethapyr, 78.2–106.1% and 82.7–104.7% for *R*-imazethapyr, 71.3–108.6% and 73–106.4% for *S*-imazamox, and 67.7–108.2% and 69.6–104.2% for *R*-imazamox. These results show that the method has good precision and accuracy for analyzing the enantiomers of imazethapyr, imazamox, and imazapic in food matrices.

Application

To determine the authenticity and practicality of the method developed for the enantioselective determination of imazethapyr, imazamox, and imazapic, 25 authentic samples ($n = 5$ for each of soybeans, maize, wheat, peanuts, and rice) were prepared using the procedures described in the “Materials and Methods” section and analyzed by UPLC–MS/MS. All samples were purchased from local markets in Nanning (China). No IM herbicides (imazethapyr, imazamox, and imazapic) were found in any of the samples.

Conclusions

A chiral UPLC–MS/MS method was developed to separate the enantiomers of three IM herbicides for simultaneous analysis of six enantiomers at trace levels in oil crops (soybeans and peanuts) and food crops (maize, wheat, and rice). The effects of chromatographic and pretreatment conditions, such as the type and pH of the mobile phase and extractant, and the type and mass of sorbent, on the separation of imidazoline racemates were evaluated in detail. Baseline separation was achieved using a Chiralcel OJ-3R chiral column and a mixture of acetonitrile and 0.1% formic acid aqueous solution. Good average recoveries, linearity, accuracy, and precision were achieved, demonstrating that this method can be applied as a qualitative and quantitative method. This is the first simultaneous enantioselective analysis of imazethapyr, imazamox, and imazapic in food matrices that are frequently treated with these herbicides. The results confirm this method is reliable for investigating herbicides in food matrices.

Funding Information This work was supported by the Natural Science Foundation of China (31101464, 31872000).

Compliance with Ethical Standards

Conflict of Interest Rui Li declares that she has no conflict of interest. Mingfeng Hu declares that he has no conflict of interest. Kunfeng Liu

declares that he has no conflict of interest. Hui Zhang declares that she has no conflict of interest. Xuesheng Li declares that he has no conflict of interest. Huihua Tan declares that he has no conflict of interest.

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

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