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Determination of chlormequat and mepiquat in pear, tomato, and wheat flour using on-line solid-phase extraction (Prospekt) coupled with liquid chromatography–electrospray ionization tandem mass spectrometry

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Abstract

A sensitive and selective method is presented for the simultaneous analysis of the pesticides chlormequat and mepiquat at trace levels in tomato, pear, and wheat flour. The method entails direct injection of the food extract onto an on-line solid-phase extraction (SPE) instrument (Prospekt) using a strong cation-exchange resin. Analyte separation and detection is done by liquid chromatography–electrospray ionization tandem mass spectrometry (LC–ESI-MS–MS). Surrogate standards (d_9-chlormequat, d_6-mepiquat) are employed to compensate for recovery losses and potential MS–MS signal suppression. The method achieves a limit of quantification for both cationic analytes at or below 5 μg/kg, and good intra- and inter-assay precision with mean variability values <7% over a concentration range up to 195 μg/kg. This study also addresses potential analyte carry-over in an SPE on-line system, as well as the robustness of the procedure and its applicability in routine quality control operations.

Keywords: Food analysis; Solid-phase extraction; Pesticides; Chlormequat; Mepiquat

1. Introduction

In agriculture, the quaternary ammonium herbicides chlormequat [(2-chloroethyl)-trimethyl-ammonium); CQ] and mepiquat (1,1-dimethylpiperidinium; MQ) are used as plant growth regulators either individually, as mixtures, or together with other pesticides [1]. Especially CQ has attracted the attention of enforcement laboratories and regulatory agencies in Europe, reflected by numerous publications and website notifications on violative levels of residues for example in fresh pears, pear juice for infants, tomatoes, and cereals [2–5]. In fact, the *Codex Alimentarius* Commission has set maximum residue limits (MRLs) for CQ at 3 mg/kg in pears, 5 mg/kg in wheat and rye, and 10

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mg/kg in oats [6]. More stringent limits have been set in European Commission Directives for CQ, i.e. 0.5 mg/kg for pears, 0.05 mg/kg for tomatoes (currently accepted limit of detection), and 0.5–5 mg/kg for cereals [7,8]. Neither the *Codex Alimentarius* Commission nor the EU have introduced MRLs for MQ in food.

Today, the most frequently employed analytical approach to determine CQ in foods is based on hyphenated mass spectrometry (MS), such as capillary electrophoresis–mass spectrometry (CE–MS) [9,10], LC–MS [11], LC–MS–MS [12–18], and matrix-assisted laser desorption ionization mass spectrometry (MALDI–MS) [19]. In contrast to conventional procedures such as LC–UV [20], MS-based techniques enable detection of the analytes at trace levels in complex matrices, with the additional advantage of near certainty of the analytes.

High sample throughput as practiced routinely in pharmacokinetic screening is now expanding rapidly into other sectors such as the environmental and food sciences [21]. However, the majority of reports on the application of on-line SPE are described on aqueous samples for environmental monitoring purposes [18,22–33], with only a few methods encompassing food, e.g. isoniazid in milk [34], and *N*-methylcarbamates and their metabolites in fruits and vegetables [35].

In this study, we have developed an on-line SPE–LC–ESI-MS–MS method for the simultaneous determination of CQ and MQ in pear, tomato, and wheat flour. The method meets stringent EU limits for pesticides in infant foods, with the added advantage of short clean-up and analysis time. Four different SCX solid-phase resins were assessed on-line with regard to their suitability to extract both analytes. Special emphasis was placed on the versatility and robustness of automated SPE for the routine determination of trace levels of CQ and MQ residues, particularly in complex food matrices.

2. Experimental

2.1. Materials and reagents

Chlormequat (CQ) chloride and mepiquat (MQ) chloride were purchased from Dr Ehrenstorfer (Augsburg, Germany). Stable and radio-isotope labelled CQ was obtained from the same sources as referred to in an earlier study [16]. Stock and working standard solutions were prepared as described previously [16].

Acetonitrile was purchased from J.T. Baker (Phillipsburg, NJ, USA). Methanol (Lichrosolv), acetone, formic acid, acetic acid, hydrochloric acid and ammonium formate were obtained from Merck (Darmstadt, Germany). Piperidine (purity >99.5%) and d_3-iodomethane (isotopic purity >98%) were from Aldrich (Buchs, Switzerland). All other solvents or chemicals were of p.a. or HPLC grade. Water was either purified in-house or purchased from Merck (LiChrosolv).

Prospekt SPE cartridges (10×2 mm I.D.) were either commercially available (BondElut SCX, Isolute SCX, and DVB SCX) or custom filled with the sorbent LiChrolut SCX (Merck) from SPARK (Emmen, The Netherlands).

2.2. d_6-Mepiquat iodide synthesis

d_3-Iodomethane (8.9 mmol) was carefully added to 2.3 mmol piperidine pre-laid in dry acetonitrile (2 ml). The reaction mixture was heated to 55–60 °C for 30 min. After cooling to room temperature, the mixture was cooled on ice. Then, any precipitated material was filtered through Schleicher & Schuell filter paper (589, 55 mm O.D.) and washed with cold acetone. Re-crystallization from acetone afforded d_6-mepiquat iodide (0.36 mmol). The compound purity (>95%) and structure were verified by ^{1}H NMR, ^{13}C NMR, and high-resolution MS. Measured mass: 120.16637 Da, calculated mass: 120.1559 Da. The isotopic purity of d_6-mepiquat was determined as >99.8 atom%.

2.3. Instrumentation

The automated SPE device consisted of an Endurance autosampler, a high pressure dispenser, and one automated cartridge exchange unit (SPARK). The SPE unit was coupled to an Alliance 2690 separation module (Waters, Rupperswil, Switzerland), that was connected to a Quattro LC tandem mass spectrometer (Micromass, Manchester, UK).

2.4. Pear, tomato, and wheat flour samples

Incurred and blank samples of wholemeal flour, fresh pears and tomatoes (fresh or canned) were purchased from various retail outlets in Switzerland.

2.5. Sample preparation

A portion (10 g) of homogenized sample was fortified with d_9-CQ and d_6-MQ as surrogate standards to achieve a final concentration of 31.5 and 19.5 μg/kg, respectively. The sample material was suspended in 100 ml of a water–methanol mixture (MeOH–H_2O, 1:1, v/v) and stirred magnetically (20 min) and subsequently centrifuged (3633 *g*, 5 min) at ambient temperature. Finally, an aliquot of the supernatant was filtered through a Millex FG syringe filter unit (0.2 μm pore size, Millipore, Bedford, MA, USA).

For the wheat flour analysis, the same procedure was performed except for the extraction step that encompassed suspension in 45 ml of water, pH adjustment to 4 with formic acid (2 *M*), and addition of methanol to a final volume of 100 ml. Furthermore, the supernatant obtained after centrifugation was placed in a freezer (−20 °C) for 1 h.

2.6. On-line SPE–LC–ESI-MS–MS

The SPE sorbent was washed and equilibrated consecutively with MeOH (2 ml), water (2 ml), and 10 m*M* HCl (4 ml). The sample extract (30 μl) was transferred by 2 ml of MeOH–H_2O (1:1, v/v) onto the SPE cartridge that was subsequently flushed with acetonitrile (2 ml) and MeOH–H_2O (1:1, v/v; 1 ml). The flow-rate was set to 4 ml/min for all cycle steps. The retained analytes were eluted with 150 m*M* ammonium formate in MeOH–H_2O (1:1, v/v, no pH adjustment) directly onto the analytical GromSil SCX column (5 μm particle size, 50×2 mm I.D., Grom Analytik & HPLC, Herrenberg-Kayh, Germany). The elution mode was isocratic at a flow-rate of 0.3 ml/min (backpressure: 48–52 bar). The column temperature was set to 35 °C. To avoid potential carry-over of residual analytes to the following SPE cartridge, the autosampler injection needle and sample loop were washed with 0.5 ml of MeOH–H_2O (1:1, v/v) containing 1% acetic acid.

Data acquisition was done in the positive ESI mode for 7 min per run. Multiple reaction monitoring (MRM) traces, cone voltages, and collision energies are listed in Table 1. The mass window was set to *m/z* 0.2 and the dwell time to 0.25 min. The needle voltage was typically set to 3.1 kV, the RF lens voltage to 0.2 V, and the ion energy for both quadrupoles to 1.0 V. The source block and desolvation temperatures were set at 120 and 400 °C, respectively. Nitrogen was used as nebulizer (90 l/h) and desolvation gas (650 l/h) and argon as collision gas (vacuum pressure: 1.7 mTorr).

2.7. Determination of the CQ extraction recovery using a ^{14}C-labelled standard

Absolute recoveries using radio isotope-labelled CQ was determined as described elsewhere [16], except that elution of the analyte was accomplished with 125 m*M* ammonium formate in MeOH–H_2O (1:1, v/v, pH not adjusted).

2.8. Quantitation

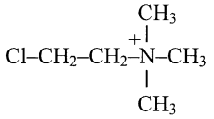
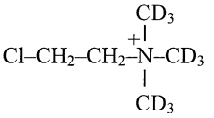
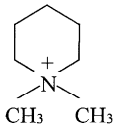
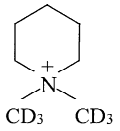
Calibration curves (five-point) were established using spiked matrix standards at concentrations between 7.8 and 195 μg/kg for CQ, and between 7.6 and 190 μg/kg for MQ. Quantitation was performed as described elsewhere [16] using the MRM traces *m/z* 122→58 for CQ, *m/z* 114→98 for MQ, and the corresponding transitions for the surrogate standards.

3. Results and discussion

3.1. LC–ESI-MS–MS

The transfer of the same chromatographic conditions previously developed in our laboratory [16] to the on-line SPE system resulted in a retention time for CQ of 6.5 min. To reduce the total duration of the analytical run, LC solvents of varying ionic strengths of ammonium acetate were assessed. However, we observed a loss of signal intensity at higher salt concentrations due to precipitation in the MS ion source region over longer periods of operation (2–3 days). The substitution of ammonium acetate with the more volatile ammonium formate circumvented

Table 1
Molecular and fragment structures as well as compound-specific ESI–MS–MS parameters used in this study

Analyte	Molecular structure	Fragment structure	MRM trace (m/z)	Cone voltage [V]	Collision energy [eV]
Chlormequat		m/z 58 $[N(CH_3)_2)CH_2]^+$ m/z 63 $[ClCH_2CH_2]^+$	122→58[a] 122→63[a] 124→58[b]	35	−30 −20 −30
d_9-Chlormequat		m/z 66 $[N(CD_3)_2)CD_2]^+$	131→66	35	−30
Mepiquat		m/z 98 $[NCH_3CH(CH_2)_4]^+$ m/z 99 $[NCH_3(CH_2)_5]^+$ m/z 58 $[N(CH_3)_2)CH_2]^+$	114→98 114→99 114→58	39	−27 −22 −25
d_6-Mepiquat		m/z 101 $[NCD_3CH(CH_2)_4]^+$	120→101	39	−27

[a] ^{35}Cl isotope.
[b] ^{37}Cl isotope.

this problem. Thus, all analyses were performed using a LC mobile phase composed of 150 m*M* ammonium formate in water–methanol (1:1, v/v) that led to significantly reduced retention times of 2.5 and 3.6 min for CQ and MQ, respectively. The ESI–MS–MS acquisition mode [16,36] complies with the MS confirmation criteria recommended by 1999/333/EG and the Commission Decision 93/256/EEC [37,38]. The corresponding molecular and product ion structures of CQ and MQ are shown in Table 1.

3.2. Sample preparation

The target analytes were extracted with a mixture of methanol–water (1:1, v/v), which was intended as a common extraction procedure for several types of food matrices (dry, fatty, watery). The more acidic extracts of tomato and pear exhibited a relatively higher MS signal response for CQ and MQ than did extracts of wheat flour (data not shown). For this reason, the pH of the aqueous wheat flour suspension was adjusted to 4.0 with formic acid before the addition of MeOH. The removal of a white precipitate (probably amylose) that formed during short storage of the extract at approximately −20 °C also improved the peak shape, leading to an increased signal intensity for both analytes.

3.3. Automated SPE procedure

A number of key parameters were assessed in on-line work to select and validate an appropriate SPE procedure. For this purpose, blank samples of pear, tomato, and wheat flour were fortified each at a level of 38 μg/kg MQ and 39 μg/kg CQ. First, SPE cartridges containing commercially available resins (BondElut SCX, Isolute SCX, DVB SCX, and LiChrolut SCX) were tested for analyte extraction efficiency. As clearly demonstrated for the wheat

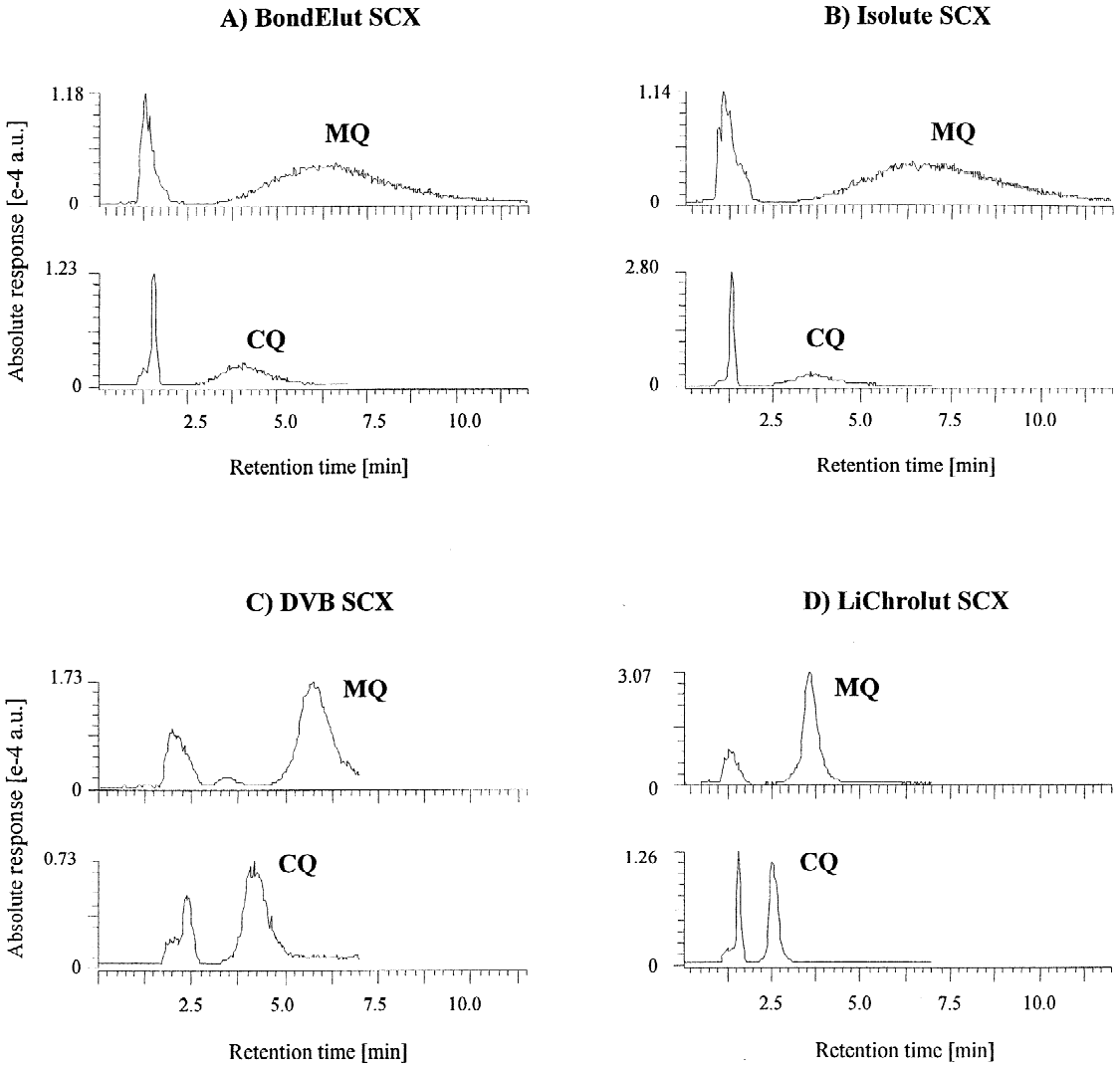


Fig. 1. SPE–LC–MS–MS traces obtained from a wholemeal wheat flour sample fortified with 39 μg/kg CQ (m/z 124→58) and 38 μg/kg MQ (m/z 114→98) using. The Prospekt SPE cartridges were filled with (A) BondElut SCX, (B) Isolute SCX, (C) DBV SCX, and (D) LiChrolut SCX.

flour sample in Fig. 1, the resins BondElut SCX and Isolute SCX showed strong retention of both CQ and MQ, resulting in very broad signals. Probably the free silanol groups in the BondElut SCX and Isolute SCX resins (not end-capped) enable polar secondary interactions that enhance the analyte retention as previously reported for certain quaternary ammonium herbicides [12,20]. The LiChrolut SCX sorbent proved the most superior and enables better accessibility and thus potentially more efficient exchange (ad- and desorption) of the analytes (Fig. 1D). Initially, the option to eliminate the LC column was considered and subsequent trials conducted, since this would shorten and simplify the analytical procedure. However, a significant loss of signal intensity was observed most probably due to ion suppression that was induced by co-eluting matrix constituents.

In the course of optimization of the SPE parameters, we also assessed the impact of the applied sample extract volume on the absolute MS signal

response. A large injection volume has the advantage of achieving a lower detection limit. Indeed, trendline slopes generated from the MS response versus injected volume showed an affect of the injected extract volume on the signal response for MQ [slope: 0.79 (pear), 0.93 (tomato), 0.89 (wheat flour)], and even more pronounced for CQ [slopes: 0.34 (pear), 0.67 (tomato), 0.75 (wheat flour)]. Based on this observation, a volume of 30 μl was injected for validation purposes.

A potential setback of on-line systems are carry-over effects [21], investigated by injecting 100 μl of MeOH–H_2O (1:1, v/v) containing 1% acetic acid after the application of a matrix sample containing 0.78 mg/kg of CQ. In this case, a system contamination of less than 0.5% was observed. Therefore, no additional rinse procedure was performed, but it may be prudent to re-inject a suspect positive sample when preceded by a sample of exceedingly high levels (concentration difference of two to three orders of magnitude). However, overload of the SPE cartridge was observed in samples fortified at an analyte level of >0.78 mg/kg.

The effect of the repeated use (n=13) of a SPE cartridge on the analyte retention time, signal shape, and response area was also determined, although this practice is not recommended in an analytical laboratory operating under good laboratory practice (GLP). For all three matrices, no shift in the retention time (RT) was observed [RT standard deviation SD_{max} 1.01% (CQ), 0.7% (MQ)]. Maximum standard deviations ranged from 3.4 to 5.7% for the absolute responses of CQ (m/z 122→58) and MQ (m/z 114→98), except for CQ in the wheat flour extract (8.1%). As illustrated in Fig. 2, the multiple injections on the same SPE cartridge had a significant effect on the signal shapes of CQ (and MQ), especially in pear, and tomato samples (data not shown).

3.4. Calibration and method performance

As described previously [16], matrix-matched calibration was required due to varying impacts of the matrices on the MS ionization efficiency. All calibration curves displayed linearity over the dynamic range, with coefficients of determination (r^2) >0.999 and >0.996 for CQ and MQ, respectively.

The limits of confirmation for CQ and MQ were below 6 μg/kg in all three matrices tested, and especially good sensitivity (<3 μg/kg) at all three mass transitions was achieved in tomato and pear samples (Table 2). Notably, the calculation of the detection limit is based on the signal-to-noise ratio of 3:1 using the MRM trace providing the lowest signal response for each analyte. The limits of quantitation

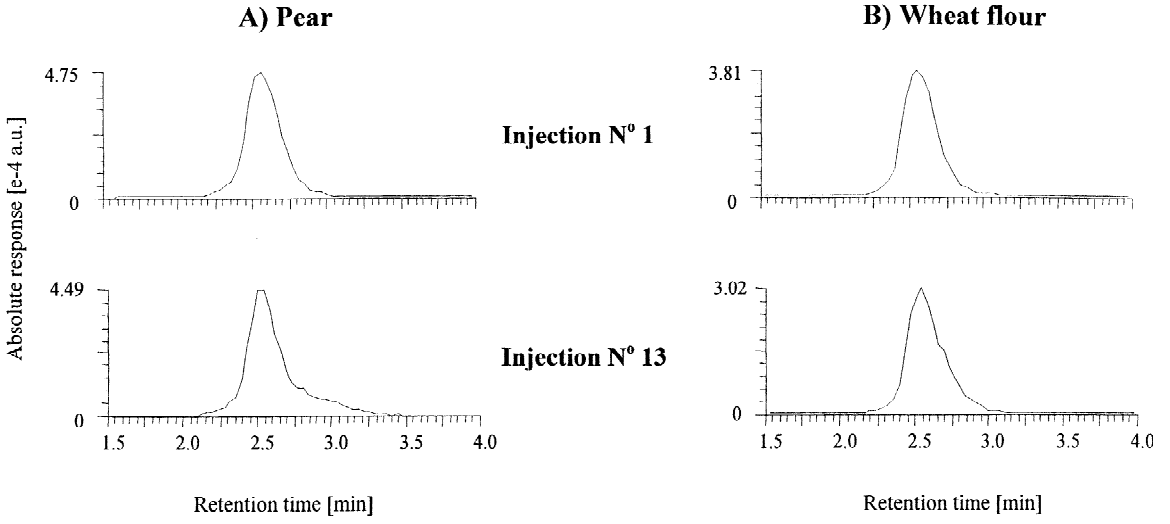


Fig. 2. SPE–LC–MS–MS traces obtained after the multiple re-use of the same LiChrolut SCX cartridge for the determination of CQ (39 μg/kg, m/z 122→58) added to (A) pear and (B) wheat flour.

Table 2
Performance characteristics of the on-line SPE–LC–ESI-MS–MS method for the determination of CQ and MQ in pear, tomato, and wheat flour

	CQ				MQ			
	m/z Trace	Pear	Tomato	Wheat flour	*m/z* Trace	Pear	Tomato	Wheat flour
Limit of confirmation [μg/kg]	124→58	1	<1	6	114→99	3	2	3
Limit of quantitation[a] [μg/kg]	122→58	1	<1	5	114→98	3	<1	3
Intra-assay C.V.[b] [%]	122→58	1.1–3.0	1.7–4.0	3.1–4.1	114→98	2.0–3.5	3.0–8.6	3.1–6.2
Inter-assay C.V.[c] [%]	122→58							
Incurred samples		3.6[d]	2.8[e]	6.8[f]/6.2[g]	114→98			
Fortified samples		1.7[h]	3.3[h]			1.8[i]	5.6[i]	3.4[i]

[a] Ten replicates, except for CQ (n=9) and MQ (n=8) in wheat flour.
[b] MQ/CQ levels [μg/kg]: 7.6/7.8, 15.2/15.6, 38/39, and 190/195; each eight replicates.
[c] df=10, except for wheat flour df=8.
[d] 3.8 μg/kg.
[e] 26.1 μg/kg.
[f] 12.1 μg/kg.
[g] 24.0 μg/kg.
[h] 15.2 μg/kg.
[i] 15.6 μg/kg.

(LOQ) were estimated according to the equation ''mean blank response+10 SD'', evaluating the data obtained from the MRM traces showing the most intense response.

Intra-assay precision was calculated with results obtained from matrix samples fortified with the target analytes at levels between 7.6 and 195 μg/kg. All three food matrices revealed variations <10%, and mean variation levels over the range tested <7% for both analytes, reflecting good method precision (Table 2). An inter-assay precision of 2.8–6.8% was achieved for CQ present in incurred samples (Fig. 3). Comparable precision values were obtained for MQ, but in this case, no incurred food samples were available, and thus measurements were performed on fortified blank samples. The closeness of the precision values obtained from the incurred and fortified samples (CQ) demonstrates good method performance, even at the very low part-per-billion level.

Introduction of the isotope-labelled standards into the SPE effluent simultaneously with the eluting analytes would have enabled a reliable determination of the analyte recovery, which was not feasible with the instrument configuration used in this study. Thus, the recovery of CQ was determined off-line after the SPE step using ^{14}C-labelled CQ. Absolute recoveries of CQ in tomatoes and wheat flour were comparable to results reported earlier in pears and cereals [16], i.e. above 90% at all spiking ranges (8.15–408 μg/kg). When averaged over the whole spiking range, recoveries in tomatoes and wheat flour of 92% (C.V. 3.7%) and 96% (C.V. 6%) were recorded, respectively.

4. Conclusion

A fully automated SPE–LC–ESI-MS–MS method has been established that enables the quantitative and confirmatory determination of CQ and MQ in pear, tomato, and wheat flour in routine quality control operations. After sample extraction, the presence of both target analytes can be assessed in less than 15 min, achieving trace level detection with good method precision and accuracy by employing isotope labeled surrogate standards.

An important limitation of the automated on-line SPE device is the potential overload of the SPE cartridge when injecting sample extracts with analyte concentrations above 0.78 mg/kg. However, this drawback can be avoided by diluting the sample extract or injecting smaller extract volumes. In this context, the rationale of residue testing must be defined, since methods need not necessarily be validated at analyte levels ''as low as possible'', but rather as low as deemed practical. For example, the

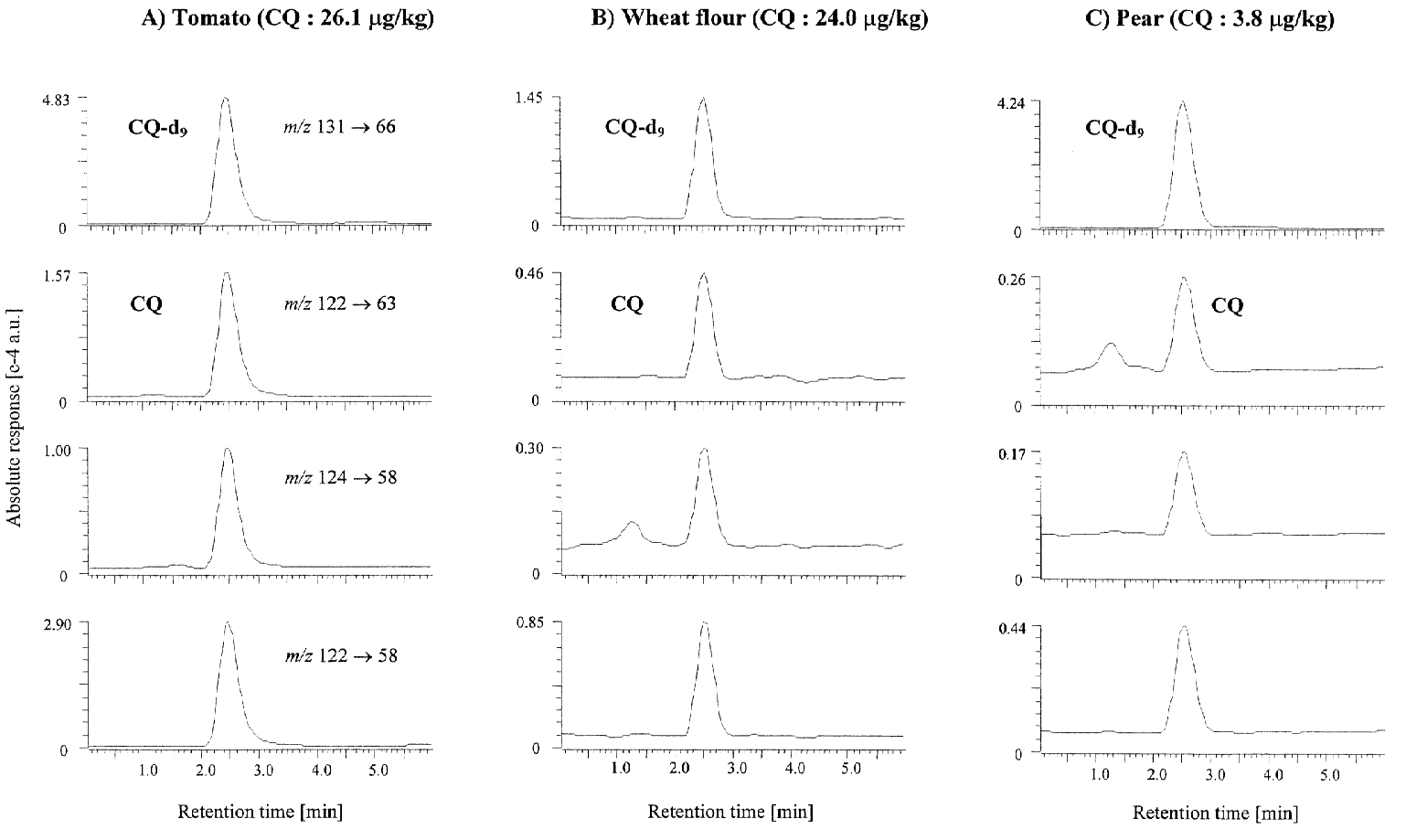


Fig. 3. SPE–LC–MS–MS traces obtained from CQ incurred samples of (A) tomato, (B) wheat, and (C) pear.

EU MRL of CQ in pears is set at 0.5 mg/kg, and thus it may be more facile to adapt the method for limits at or around this value. In case of monitoring CQ and MQ at ''blanket levels'' of 0.01 mg/kg in raw material that is intended for the production of infant food [39,40], the method performance should be ideally determined with samples contaminated at the very low part-per-billion level.

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