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Rapid Determination of Chlormequat in Meat by Dispersive Solid-Phase Extraction and Hydrophilic Interaction Liquid Chromatography (HILIC)−Electrospray Tandem Mass Spectrometry

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Supporting Information

ABSTRACT: A rapid method for analyzing trace levels of chlormequat (CQ) in meat samples by hydrophilic interaction liquid chromatography (HILIC)−electrospray tandem mass spectrometry was developed. The samples were extracted with acetonitrile, followed by a rapid cleanup through a dispersive solid-phase extraction (DSPE) technique with octadecyl (C18) DSPE sorbents. The chromatographic separation was achieved within 6 min using a HILIC column with 10 mM ammonium acetate and 0.1% (v/v) formic acid in water/acetonitrile (v/v, 40:60) as the mobile phase. Quantification was performed using a matrix-matched calibration curve, which was linear in the range of the 0.05−100 μg/L. The limit of detection (LOD) was estimated at 0.03 μg/kg for CQ on the basis of a peak to peak signal noise (S/N = 3). The limit of quantification (LOQ) was 0.1 μg/kg on the basis of the lowest spiked concentration with suitable precision and accuracy. The average recovery of CQ in spiked meat samples was 86.4−94.7% at 2, 20, and 200 μg/kg. Finally, this method was applied to determine CQ in the livestock and poultry meats purchased from markets in Beijing in 2011. CQ was detected in all 12 samples, and the concentration was 0.4−636.0 μg/kg. Concentrations in a chicken sample (636.0 μg/kg) and a goat meat sample (486.0 μg/kg) were found to be 15.9 and 2.43 times the corresponding Codex maximum residue limits, respectively.

KEYWORDS: *chlormequat chloride, meat, HILIC, LC-MS/MS, dispersive solid-phase extraction*

INTRODUCTION

Chlormequat (CQ) chloride is an important gibberellin biosynthesis inhibitor, which is widely used as a plant growth regulator to reduce longitudinal shoot growth and improve yields of the crop in modern agriculture.[1−4] It is reported that the annual CQ production is in excess of 10000 tons in China, and by far, it is still the most widespread plant growth regulator in the European Union.[5−7] In recent years, considerable attention has been focused on the residues of CQ in foods, because of its reproductive and developmental toxicities and suspected endocrine disruption to animals.[7−13] Therefore, the majority of countries regulate the application of CQ strictly. For example, CQ is registered for use on only ornamental plants, but prohibited in food/feed uses in the United States. Codex has set maximum residue levels (MRLs) for CQ in feed and some foods, such as 3000 μg/kg in wheat, 200 μg/kg in goat meat, and 40 μg/kg in poultry meat.[14]

Owing to the low levels in the tissues of the foods of animal origin and the complexity of biosample matrices, the analysis of CQ is a challenging task. This implies that an effective sample preparation process and sensitive analytical instruments are necessary to achieve the optimal sensitivity, selectivity, and specificity. To the best of our knowledge, only one study has been published about the determination of CQ in animal tissues in a JMPR (the joint FAO/WHO meetings on pesticide residues) report,[15] in which Weidenauer used ion-pair chromatography coupled with a conductivity detector to determine CQ in fortified poultry and dairy cow products after cleanup by a cation exchange column and an alumina column. This method involves a lengthy and tedious cleanup process, with poor reproducibility, and the limit of quantification (LOQ) (50 μg/kg) was insufficient to meet the requirement of the MRLs for CQ in chicken (40 μg/kg) by Codex.

Dispersive solid-phase extraction (DSPE),[16] one of the most promising sample preparation techniques, is based on the addition of a small amount of SPE sorbent into the extract to remove the matrix coextractives.[17,18] In recent years, DSPE has been successfully used for the extraction and purification of chemicals in animal tissues, such as pesticides,[19] polycyclic aromatic hydrocarbons,[20] polybrominated diphenyl ethers,[21] and veterinary drugs.[22−25]

In this study, we developed a rapid and sensitive method for analyzing CQ in meat using DSPE and LC-MS/MS by applying a

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hydrophilic interaction liquid chromatography (HILIC) column. It was applied to the analysis of CQ in goat meat, beef, pork, and chicken samples purchased from markets in Beijing, China.

EXPERIMENTAL PROCEDURES

Chemicals and Reagents. CQ (99 ± 0.5%) and d_4-CQ (100 mg/L) were purchased from Dr. Ehrenstorfer GmbH (Augsburg, Germany). HPLC grade acetonitrile was from Fisher Chemical Co. (Somerville, NJ, USA), and formic acid (99.7%) and ammonium acetate were from Dima Technology Inc. (Richmond, USA). Primary secondary amine (PSA), octadecyl (C18), and graphitized carbon black (GCB) sorbents were obtained from Agela Technologies (Beijing, China). Sodium sulfate anhydrous (Beijing, China) was of analytical grade and was heated at 450 °C for at least 4 h, naturally cooled, and stored in desiccators. Ultrapure water was produced by a Milli-Q RC apparatus (Millipore, Bedford, MA, USA). Stock standard solutions of CQ (5.0 g/L) and d_4-CQ (10.0 mg/L) were prepared in acetonitrile, and the working solutions of the individual standards and mixtures of both of them were obtained by appropriate dilution with acetonitrile. All of the solutions were stored at −20 °C.

Instruments and Chromatographic Conditions. Chromatographic analyses were conducted using an Agilent series 1200 HPLC system (Agilent, Santa Clara, CA, USA) equipped with a binary pump, a column oven, and an autosampler. CQ was separated using an XBridge HILIC column (150 mm × 2.1 mm × 3.5 μm) (Waters, Ireland) at 40 °C, and the injection volume was 5 μL. Aqueous solutions containing 0.1% formic acid and 10 mM ammonium acetate (A) and acetonitrile (B) were used as the mobile phase. The isocratic elution was carried with 60% B at a flow rate of 0.1 mL/min.

The mass spectrometric detection was operated using an API 5000 tandem quadrupole mass spectrometer (Applied Biosystems, Foster City, CA, USA) in the positive ionization mode with multiple-reaction monitoring (MRM). Typical parameters of the electrospray ionization source (ESI) were as follows: source temperature (TEM), 500 °C; ion spray voltage (IS), 5500 V; curtain gas pressure (CUR), 30 psi; collision gas (CAD), 4 V; atomization air pressure (GS_1), 50 psi; auxiliary gas (GS_2), 55 psi; dwell time, 200 ms; resolution Q1, low; resolution Q2, unit; entrance potential (EP), 11 V; declustering potential (DP), 36 V; and collision cell exit potential (CXP), 7 V. The MRM transitions and collision energy (CE) applied are summarized in Table 1. All system control, data acquisition, and data analysis were performed with AB Sciex Analyst 1.4.2 software (Applied Bioscience).

Table 1. Retention Time and Optimized MS/MS Parameters of CQ and d_4-CQ

analyte	RT (min)	precursor ion (m/z)	qualifier ion (m/z)	CE (V)
CQ	5.34	122.1	58.1[a]	40
			63.1	29
d_4-CQ	5.34	126.1	58.1[a]	40
			67.1	29

[a]Quantifier ion.

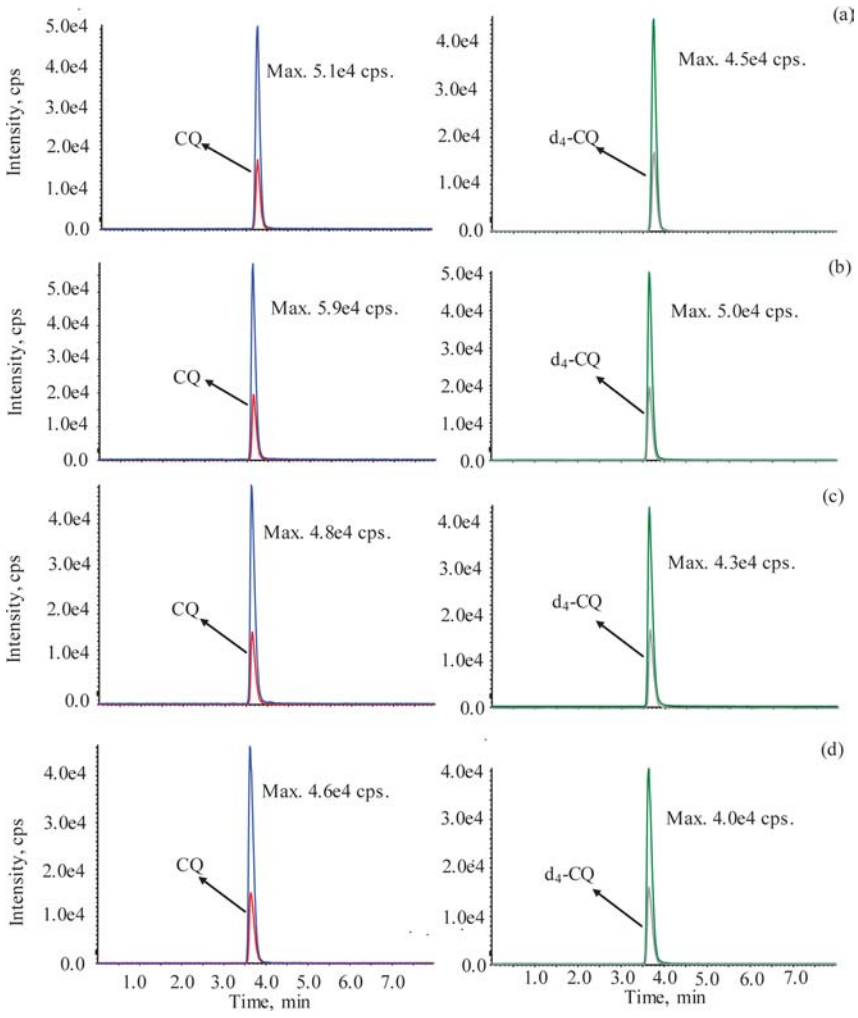

Figure 1. MRM chromatograms of standard of CQ (1.0 μg/L) and d_4-CQ (1.0 μg/L) at different percentages of formic acid in the aqueous phase: (a) 0.05%; (b) 0.1%; (c) 0.2%; (d) 0.5%.

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Sample Preparation. Goat meat, beef, chicken, and pork samples were purchased from supermarkets and a wholesale market in Beijing, China, in November 2011 and stored at −20 °C prior to analysis. Organic goat meat, beef, chicken, and pork free from CQ were directly from certified enterprises by the third-party certification (TPC) and used as a reference blank matrix for development of the method.

Frozen meat samples were first thawed for about 30 min, then cut into slices, ground, and homogenized using an analytical mill (IKA, Germany). A well-homogenized sample (0.5 g wet weight) was spiked with 200 μL of 500 μg/L d_4-CQ as a recovery surrogate and equilibrated for 1 h. After that, the spiked sample was ground with 4.0 g of sodium sulfate anhydrous in an agate mortar, and the mixture was transferred to a 50 mL plastic centrifuge tube with 100 mg of C18 DSPE sorbents. After the addition of 10 mL of acetonitrile, the tube was sonicated for 10 min and centrifuged for 5 min (10000 rpm and 4 °C). The clarified supernatant was collected in an evaporation flask. The procedures described above were repeated once again. Finally, the combined supernatants were rotoevaporated, and the residues were dried under a gentle nitrogen stream and reconstituted with 1 mL of an acetonitrile/water (v/v, 60:40) solution for LC-MS/MS analysis. For all samples, the final concentration of d_4-CQ was 100 μg/L.

Method Validation. The method was validated for calibration, recovery, and precision according to the guidance document on pesticide residue analytical methods.[26] Identification of CQ in meat was accomplished by comparing the retention time with the corresponding standard (within 2%), and each sample was analyzed three times ($n = 3$). The seven-point calibration curve was constructed for the matrix-matched standard solutions in a concentration range between 0.05 and 100 μg/L for quantification. Recoveries were evaluated by spiking solutions to blank meat samples at three concentration levels of 2, 20, and 200 μg/kg for CQ. The precision of the method for CQ was evaluated by intra- and interday precision and relative standard deviation (RSD). The limit of detection (LOD) and limit of quantification (LOQ) of CQ were evaluated by analyzing spiked samples at the lowest concentration in spiked recovery experiments with signal-to-noise (S/N) ratios at 3 and 10, respectively.

RESULTS AND DISCUSSION

Liquid Chromatography Optimization. The acidity of the mobile phase was a critical factor for resolution and response on the HILIC column.[27−33] Figure 1 shows the MRM chromatograms of CQ and d_4-CQ standard solutions (1.0 μg/L) obtained at the different percentages of formic acid varied from 0.05 to 0.5% in the aqueous phase. As shown in Figure 1, the retention of CQ slightly decreased with the percentage of formic acid increasing from 0.05 to 0.5%, whereas the response was observed as a wave pattern with the highest response occurring at the percentage of 0.1% for formic acid. Considering the retention and sensitivity, 0.1% formic acid was chosen. However, the bad peak shape and a large drift of retention time for CQ occurred in a matrix-matched solution and a spiked sample solution when the aqueous phase consisting of only 0.1% formic acid was used (Figure 2a,b). Compared to the chromatogram of the corresponding standard in acetonitrile, the largest drift of retention time of CQ could reach about 2 min (Figure 2c). Hemström and Irgum found ionic strength seems to play an important role in HILIC separations, and the use of buffered eluents can reduce the electrostatic interations between charged analytes and deprotonated silanol groups of the stationary phase in HILIC.[28] Therefore, to solve the above problems, ammonium acetate was also added into the aqueous phase. The effect of different concentrations of ammonium acetate was evaluated. Figure 3 shows the MRM chromatograms of CQ and d_4-CQ in matrix-matched standard (0.5 μg/L) obtained at different concentrations of ammonium acetate between 5 and 50 mM. As shown in Figure 3, the highest response occurred when the concentration of ammonium acetate was 10 mM, although the strongest retention was observed at 5 mM. As a result, an aqueous solution containing 0.1% formic acid and 10 mM ammonium acetate was selected as the mobile phase in this study.

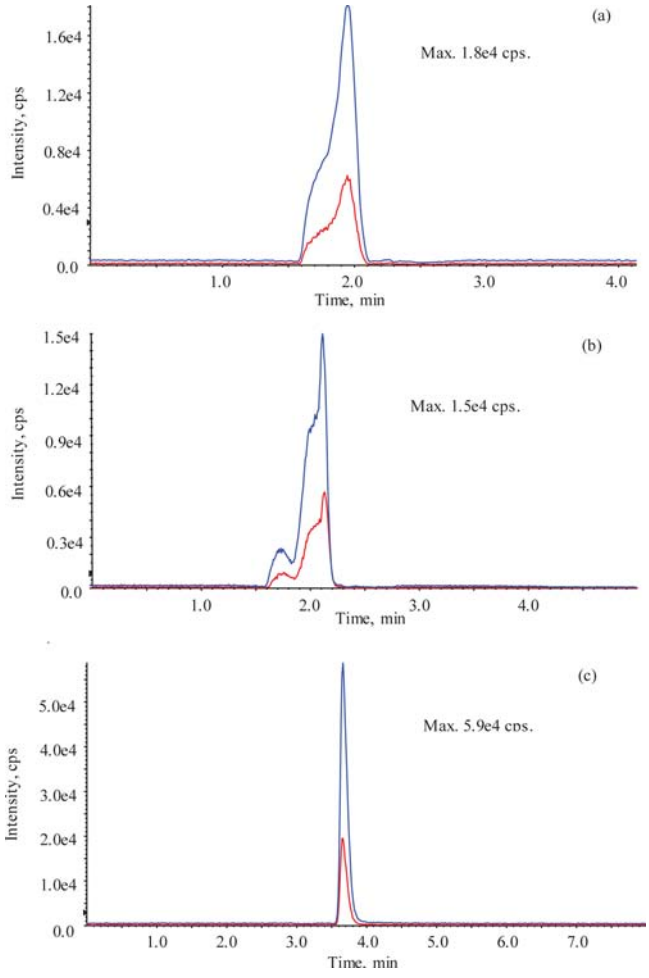

Figure 2. MRM chromatograms of CQ (1.0 μg/L) in (a) matrix-matched solution, (b) spiked sample solution, and (c) standard solution, when the aqueous phase consisted of only 0.1% formic acid.

Sample Preparation Optimization. The effects of different DSPE sorbents such as PSA, GCB, and C18 were compared in this study. As shown in Figure 4a, the mean recovery was obtained at 32.6% for CQ when 100 mg of PSA was used as DSPE sorbent, although the PSA was a common sorbent to remove various polar organic acids and fatty acids.[34−36] A similar result was observed by using 100 mg of GCB as DSPE sorbent; the poor recovery was 43.5% for CQ. Satisfactory recovery (94.7%) was obtained by using 100 mg of C18 as DSPE sorbent. C18 cleanup using acetonitrile was documented to retain the interference for alkylphenol and organochlorine pesticides successfully in biota samples.[37,38] Schmitz-Afonso et al.[38] used a SPE cleanup based on the C18 procedure to remove oil and pigment in the extracts of osprey eggs from the Chesapeake Bay area. Then, the effect of different amounts of C18 sorbents on recovery was further optimized to range from 0 to 500 mg. As shown in Figure 4b, the optimal mean recovery was observed at 94.7% by adding 100 mg of C18. Therefore, 100 mg of C18 was chosen as the DSPE sorbent in this study.

Matrix Effect. Matrix effects were calculated by building calibration curves ($n = 7$) for CQ and d_4-CQ with standards in

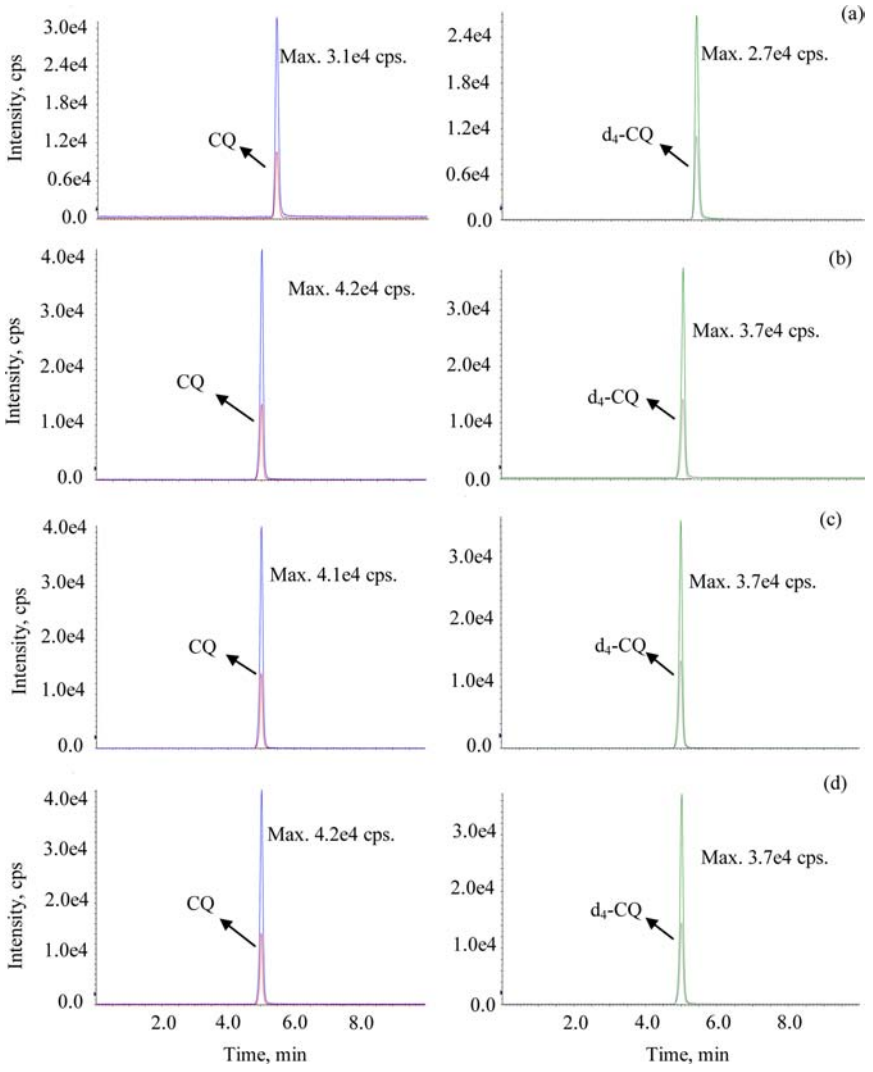

Figure 3. MRM chromatograms of matrix-matched standard of CQ (0.5 μg/L) and d_4-CQ (0.5 μg/L) at different concentrations of ammonium acetate added to the aqueous solution containing 0.1% formic acid: (a) 5 mM; (b) 10 mM; (c) 20 mM; (d) 50 mM.

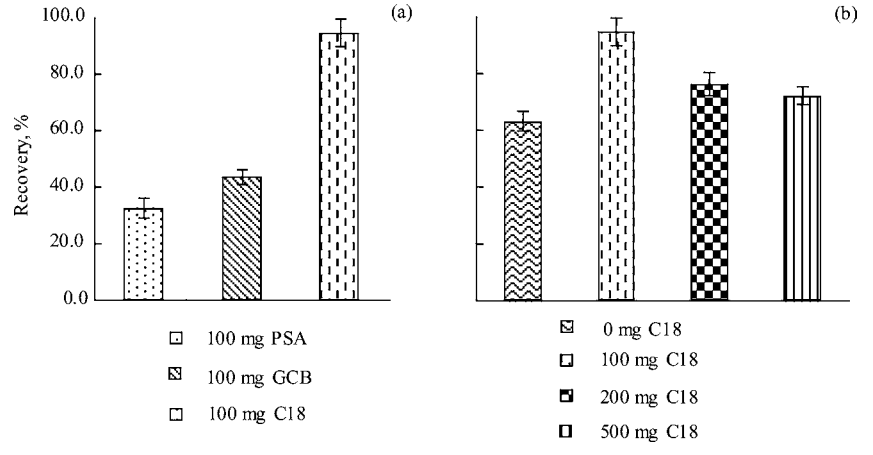

Figure 4. Effect of (a) different DSPE sorbents and (b) different amounts of C18 sorbents on the recovery of CQ spiked at 200 μg/kg in blank goat meat samples.

solvent and blank extracts of the corresponding matrix. As shown in Table 2 and Figure S1 of the Supporting Information, significant suppression matrix effects were observed in pork, beef, and goat meat samples, because calibration curves in the matrix had lower slopes than calibration curves in the solvent, which were similar to the results of CQ in apple and tomato reported by Xue et al.[39] However, slight suppression matrix effects were observed in chicken. Therefore, in the quantification of samples, calibration curves were built by spiking blank extracts of the corresponding matrix to reduce the influence of the matrix.

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Table 2. Matrix Effect on the Responses of CQ and d_4-CQ

	slopes of solvent and matrix linear curves		r^2	
	CQ	d_4-CQ	CQ	d_4-CQ
solvent	2.3×10^5	2.7×10^5	0.9997	0.9996
goat meat	1.5×10^5	1.8×10^5	0.9945	0.9949
beef	1.9×10^5	2.4×10^5	0.9956	0.9967
pork	1.5×10^5	1.8×10^5	0.9926	0.9912
chicken	2.2×10^5	2.6×10^5	0.9947	0.9930

Table 3. Mean Recoveries, LODs, and LOQs, and Intra- and Interday RSDs for CQ in Blank Goat Meat Samples (n = 3)

spiking level (μg/kg)	mean recovery (%) (RSD %)	LOD (μg/kg)	LOQ (μg/kg)	intraday RSD %	interday RSD %
2	89.9 (3.7)	0.03	0.1	2.1	11.8
20	86.4 (5.7)			0.8	13.4
200	94.7 (4.9)			1.7	14.2

Table 4. Concentrations of CQ in Meat Samples from Markets in Beijing in 2011 (n = 3)

sample no.	mean detected level (μg/kg)	RSD (%)	CAC[a]/MRL (μg/kg)
goat meat			
1	14.4	1.9	200
2	486.0	1.5	
3	32.6	1.1	
beef			
1	0.8	0.9	200
2	27.8	1.5	
3	0.6	1.7	
pork			
1	19.5	0.8	200
2	0.4	1.5	
3	20.6	2.1	
chicken			
1	0.8	1.6	40
2	636.0	0.8	
3	0.5	1.7	

[a]CAC, Codex Alimentarius Commission.

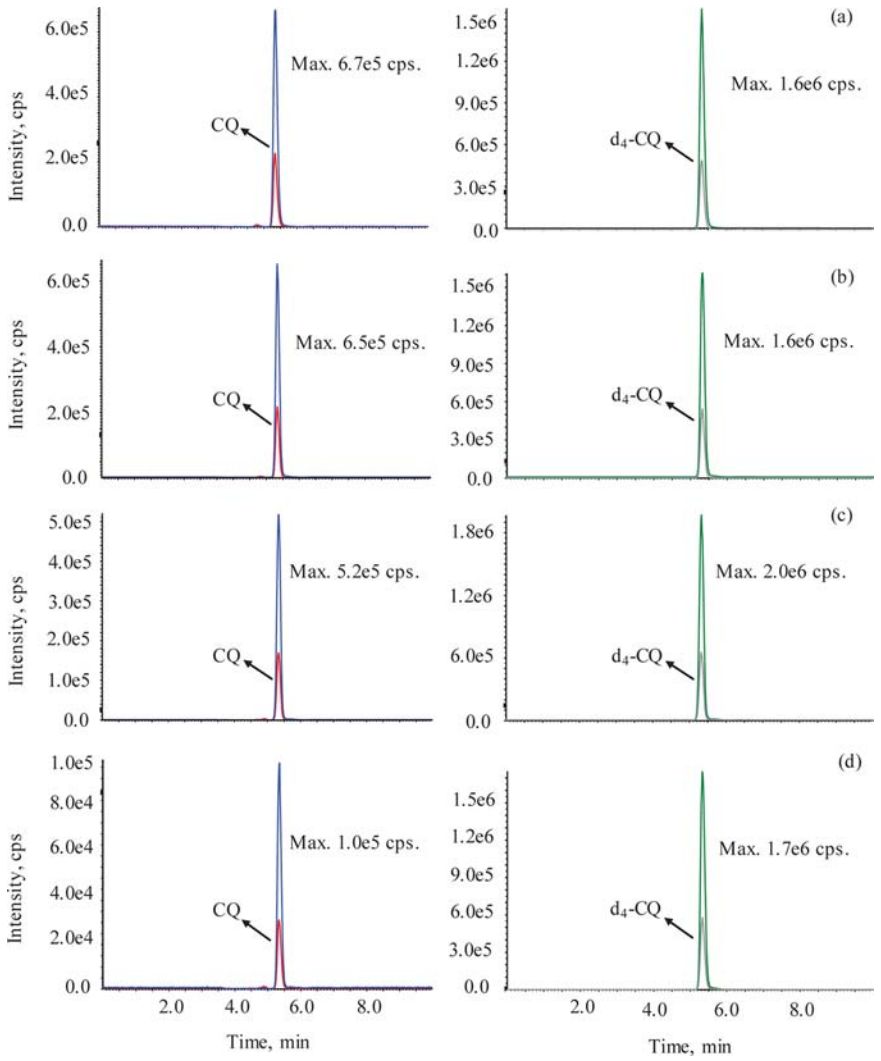

Figure 5. MRM chromatograms of CQ in four meat samples (spiked with d_4-CQ 200 μg/kg): (a) goat meat (CQ = 32.6 μg/kg); (b) beef (CQ = 27.8 μg/kg); (c) pork (CQ = 19.5 μg/kg); (d) chicken (CQ = 0.5 μg/kg).

Method Validation. External calibration was applied for quantification of CQ in meat samples. The calibration curve was constructed from 0.05 to 100 μg/L of CQ in the matrix-matched standard solutions. Calibration graphs were linear with a good

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correlation coefficient (r^2) >0.99. The LOD of CQ was 0.03 μg/kg. The LOQ of CQ was 0.1 μg/kg, significantly lower than the Codex MRLs for CQ in meat, which indicated that the method was sensitive enough to analyze trace concentrations of CQ in meat. The LOQ was 500 times lower than that obtained using ion-pair chromatography coupled with the conductivity detector method developed by Weidenauer.[15] The intraday and interday precisions were calculated by the RSDs at three concentration levels for CQ within the linear ranges. The intraday RSDs (n = 3) were <2.2%. The interday RSDs were calculated by a 15 day period day-to-day replicated analysis and were generally <14.3%. The recovery (n = 3) of CQ in the spiked meat samples was 80.8−100.0%, and the RSDs were 3.7−5.7% (Table 3).

Application of the Method to Meat Samples. This method was applied to analyze residues of CQ in goat meat, beef, chicken, and pork samples purchased from markets in Beijing, China, in 2011. As shown in Table 4, CQ was detected in all meat samples. The concentrations of CQ in different samples ranged from 0.4 to 636.0 μg/kg, and RSDs were 0.8−2.1% (n = 3). As an example, Figure 5 shows the MRM chromatograms of CQ in the goat meat (32.6 μg/kg), beef (27.8 μg/kg), pork (19.5 μg/kg), and chicken samples (0.5 μg/kg). It should be noted that the concentrations in a chicken sample (636.0 μg/kg) and a goat meat sample (486.0 μg/kg) were found to be 15.9 and 2.43 times the corresponding Codex MRLs, respectively.

Conclusions. A rapid, specific, and sensitive method for the analysis of CQ in meat samples using LC-MS/MS with DSPE was developed. The method was successfully applied to determine CQ in goat meat, beef, chicken, and pork samples, and detectable concentrations were found in all samples. The method provides not only an approach to assess the health risk of CQ in foods of animal origin but also an approach for pharmacokinetic, toxicokinetic, and clinical studies.

■ ASSOCIATED CONTENT

Supporting Information

Figure S1. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

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