ELSEVIER

Journal of Chromatography B, 732 (1999) 55–64

JOURNAL OF CHROMATOGRAPHY B

www.elsevier.com/locate/chromb

# Simultaneous determination of residual tetracyclines in foods by high-performance liquid chromatography with atmospheric pressure chemical ionization tandem mass spectrometry

Hiroyuki Nakazawa[a,*], Shigeru Ino[a], Kayoko Kato[a], Takaho Watanabe[a], Yuko Ito[b], Hisao Oka[b]

[a]*Department of Analytical Chemistry, Faculty of Pharmaceutical Sciences, Hoshi University, 2-4-41 Ebara, Shinagawa-ku, Tokyo 142-8501, Japan*

[b]*Aichi Prefectural Institute of Public Health, 7-6 Nagare, Tsuji-machi, Kita-ku, Nagoya 462-8576, Japan*

Received 19 February 1999; received in revised form 2 June 1999; accepted 2 June 1999

**Abstract**

We established a method for precisely determining residual tetracycline antibiotics (TCs) in foods by atmospheric pressure chemical ionization liquid chromatography-tandem mass spectrometry (APCI LC–MS–MS) using selected reaction monitoring with an internal standard. By setting the nebulizer probe temperature to 475°C, we were able to use a mobile phase containing oxalic acid without clogging problems at the APCI interface, since oxalic acid decomposes to carbon dioxide and water at high temperature. DMCTC was very effective as an internal standard for determining TCs in various foods. TCs were cleaned up using a Bond Elut ENV cartridge and analysed by APCI LC–MS–MS. The recovery of TCs from various foods including animal tissues, honey, milk, eggs, and fish fortified at levels of 0.05, 0.10, and 0.50 ppm averaged 60.1–88.9%, with an RSD of 1.2–8.7%. The detection limits were 0.001 ppm for OTC and TC, 0.004 ppm for CTC, and 0.002 ppm for DC. The present method was also successfully used to determine TCs in swine kidney samples that were previously found by microbiological assay. 

*Keywords:* Tetracyclines

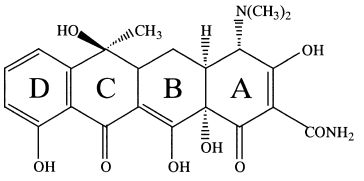
## 1. Introduction

Tetracycline antibiotics (TCs, Fig. 1), represented by oxytetracycline (OTC), tetracycline (TC), chlortetracycline (CTC), and doxycycline (DC), are commonly used worldwide as veterinary medicines and feed additives. In Japan, residual TCs have sometimes been found in animal tissues and honey [1,2]. Microbiological assays have been most commonly used to detect such residues, but they are complicated, time consuming and non-specific. In contrast, mass spectrometric techniques can confirm the presence of residual drugs with high sensitivity and selectivity [3–6]. Therefore, a method that combines a simple and precise chromatographic separation with an appropriate mass spectrometric determination may offer a significant advantage for the absolute confirmation of residual TCs.

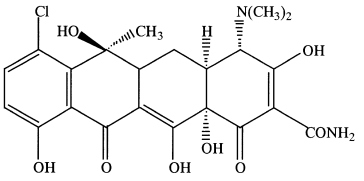
*Corresponding author. Tel.: +81-3-5498-5763; fax: +81-3-5498-5763.

*E-mail address:* nakazawa@hoshi.ac.jp (H. Nakazawa)

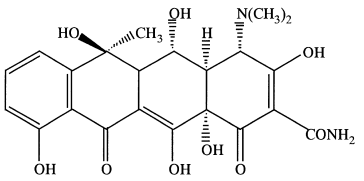
0378-4347/99/$ – see front matter 
PII: S0378-4347(99)00260-1



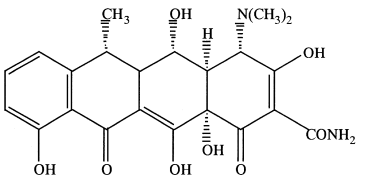

Tetracycline (TC, MW: 444)



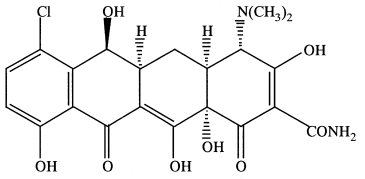

Chlortetracycline (CTC, MW: 478)




Oxytetracycline (OTC, MW: 460)




Doxycycline (DC, MW:444)




Demeclocycline (DMCTC, MW: 464)

Fig. 1. Structures of tetracycline antibiotics.

To confirm TCs in animal tissues, we previously reported an analytical method using electrospray ionization liquid chromatography tandem mass spectrometry (ESI LC–MS–MS) with a mobile phase containing trifluoroacetic acid and a well end-capped C-8 modified silica gel column [7]. However, we could not use this technique to determine residual TCs in animal tissues, because of its lack of sensitivity and reproducibility due to the co-elution of substances from samples. To overcome these problems, we needed to improve the separation between TCs and co-eluting substances on a LC column using a mobile phase containing oxalic acid, since a mobile phase containing oxalic acid provides the best separation between TCs and co-eluting substances [8]. However, mobile phases containing non-volatile compounds, when used in liquid chromatography–mass spectrometry (LC–MS), have been noted to cause clogging at the interface and a build-up of deposits in the ion source, so that ESI LC–MS cannot be performed for a prolonged period [9,10]. We considered that while oxalic acid may cause clogging at the ESI interface at room temperature, it may not cause this problem at an atmospheric pressure chemical ionization (APCI) interface above 400°C, since oxalic acid decomposes to carbon dioxide and water above 200°C.

The ionization efficiency of atmospheric pressure

ionization (API) including ESI, ion spray ionization, and APCI is greatly affected by co-eluting substances from the LC column. Therefore, we considered that the use of an internal standard is essential for API LC–MS conditions, and decided to use APCI LC–MS–MS with a mobile phase containing oxalic acid and demeclocycline (DMCTC, Fig. 1) as an internal standard to determine TCs in foods. In the present paper, we report in detail the determination of residual TCs in foods using selected reaction monitoring (SRM) with an internal standard under APCI LC–MS–MS conditions.

## 2. Experimental

### 2.1. Materials

Methanol, acetonitrile, disodium ethylenediaminetetraacetate ($Na_2EDTA$), oxalic acid, citric acid and disodium hydrogen phosphate were obtained from Wako Pure Chemicals Industries. (Osaka, Japan). The hydrochlorides of OTC, TC, CTC, DC and DMCTC were supplied by Pfizer Pharmaceuticals. (Tokyo, Japan). Standard solutions of OTC, TC, CTC, DC, and DMCTC were prepared at a concentration of 1 mg/ml in distilled water and kept at −30°C. The solutions were diluted to the required concentrations with distilled water before use.

### 2.2. Extraction and clean-up procedures

Extraction and clean-up procedures used in the present study were described in detail in our previous papers [7,8], therefore, a brief statement is given here. A sample (5 g) was blended with 20 ml of 0.1 *M* $Na_2EDTA$-McIlvaine buffer (pH 4.0) using a Polytron-Aggregate (Kinematica, Luzern, Switzerland) and then centrifuged at 770 *g* for 15 min. A further 20 ml and 10 ml of buffer were added to each of the tissue residues, and the extractions were repeated. The supernatants were combined and filtered. The filtrate was applied to a Bond Elut ENV solid-phase extraction cartridge (500 mg, 6 ml, part number 1225-5011, lot number EN3220, Varian, Harbor City, USA) that had been pretreated with methanol (5 ml) followed by water (15 ml). The cartridge was washed with 20 ml of water and air-dried by aspiration for 5 min. TCs were eluted from the column with 20 ml of methanol, and the eluate was evaporated to dryness under reduced pressure at 30°C. The residue was dissolved in 1 ml of water–methanol (50:50, v/v) containing DMCTC at a concentration of 5 μg/ml as an internal standard, and a 10 μl aliquot of the sample was injected into the LC–MS–MS system.

### 2.3. Instrument

The HPLC system consisted of a Waters 600s controller, 616 pump, 717plus autosampler, and 996 photodiode array detector. The LC–MS–MS system consisted of an API 300 triple quadrupole tandem mass spectrometer (PE-Sciex, Thornhill, Canada) equipped with a heated nebulizer interface. This system was coupled to the outlet of the HPLC column using a length of PEEK tubing.

### 2.4. Chromatographic conditions

Chromatography was performed on a Bakerbond C8 column (5 μm, 250×4.6 mm I.D., J.T. Baker Chemical, Phillipsburg) at 30°C. The mobile phase was methanol–acetonitrile–5 m*M* aqueous oxalic acid (18:27:55, v/v/v). The flow-rate and monitored wavelength were 1 ml/min and 350 nm, respectively.

### 2.5. Mass spectrometric conditions

The nebulizer probe temperature was set at 475°C, and the nebulizing gas (nitrogen) pressure and flow-rate were set at 345 kPa and 1.4 l/min, respectively. The flow-rate of heated auxiliary gas (nitrogen) and the curtain gas (nitrogen) flow-rate were set at 0.4 and 1.1 l/min, respectively. Positive chemical ionization was carried out by a corona discharge needle set at +2.5 μA. The orifice voltage was adjusted to 10 V. Collision induced dissociation (CID) experiments were performed using nitrogen and a collision offset setting of −25 V.

## 3. Results and discussion

### 3.1. APCI LC–MS–MS of TCs

#### 3.1.1. Selection of the nebulizer probe temperature

In the present study, we intended to decompose oxalic acid at the APCI interface at a temperature higher than 200°C to avoid clogging problems at the interface. The combination of an APCI interface and a mobile phase containing oxalic acid has been previously reported [11], however, we could not perform APCI LC–MS for a long time without clogging problems under the reported LC–MS conditions, since the mobile phase contains $Na_2EDTA$, which is a non-volatile salt. We investigated clogging by oxalic acid at the interface by varying the nebulizer probe temperature from 325 to 475°C. Although oxalic acid decomposed at the interface when the temperature ranged from 375 to 450°C, clogging at the interface still occurred after 2 h of operation. However, with a temperature of 475°C, we were able to operate the APCI interface continuously for 1 week without clogging problems. Therefore, we selected a nebulizer probe temperature of 475°C for subsequent work.

#### 3.1.2. MS–MS conditions

When precursor ions of TCs were set at each $[M+H]^+$ (OTC: $m/z$ 461, TC and DC: $m/z$ 445, CTC: $m/z$ 479, and DMCTC: $m/z$ 465), $[M+H-NH_3]^+$ and $[M+H-NH_3-H_2O]^+$ were observed as product ions under APCI MS–MS conditions. These ions are very characteristic for TCs, and enable us to identify TCs [7]. The loss of $NH_3$ and $H_2O$ are derived from the carboxyamide group in the A-ring and hydroxyl group in the C-ring, respectively. However, DC only gives $[M+H-NH_3]^+$, due to the lack of a hydroxyl group. The presence or absence of this ion can be used to differentiate TC from DC. Therefore, these three ions should be observed in the tandem mass spectra of TCs.

To optimize the MS–MS conditions, we carefully observed the above three product ions under two different collision offsets (−10 V and −25 V). As shown in Table 1, when the collision offset was set at −10 V, the most abundant ion was $[M+H]^+$, while the intensities of $[M+H-NH_3]^+$ and $[M+H-NH_3-H_2O]^+$ were very weak. It was difficult to identify TCs under this condition. When the collision offset was set at −25 V, the most abundant ions were $[M+H-NH_3]^+$ or $[M+H-NH_3-H_2O]^+$, and $[M+H]^+$ was also clearly observed. Therefore, we chose to use the most abundant product ion generated under an offset voltage of −25 V to determine TCs: $[M+H-NH_3-H_2O]^+$ for OTC ($m/z$ 426), TC ($m/z$ 410), and CTC ($m/z$ 444) and $[M+H-NH_3]^+$ for DC ($m/z$ 428) and DMCTC ($m/z$ 448).

#### 3.1.3. SRM of TCs

Five nanograms each of TC standard solution was injected into the LC–MS–MS system under optimal conditions. Fig. 2 shows total ion chromatogram (TIC) and SRM profiles. All of the TC peaks were clearly observed at a retention time of 7.7 min for

Table 1
Effect of offset voltage on precursor and product ions of tetracyclines

| | Precursor ions | Product ions (relative abundance) | | | | | |
|---|---|---|---|---|---|---|---|
| | | Offset voltage −10 V | | | Offset voltage −25 V | | |
| OTC | $[M+H]^+$ | 461 | 444 | 426 | 461 | 444 | 426 |
| | 461 | (100) | (21) | (14) | (2) | (18) | (100) |
| TC | $[M+H]^+$ | 445 | 428 | 410 | 445 | 428 | 410 |
| | 445 | (100) | (27) | (17) | (2) | (16) | (100) |
| CTC | $[M+H]^+$ | 479 | 462 | 444 | 479 | 462 | 444 |
| | 479 | (100) | (19) | (7) | (10) | (65) | (100) |
| DC | $[M+H]^+$ | 445 | 428 | | 445 | 428 | |
| | 445 | (100) | (30) | | (3) | (100) | |
| DMCTC | $[M+H]^+$ | 465 | 448 | 430 | 465 | 448 | 430 |
| | 465 | (100) | (26) | (4) | (7) | (100) | (68) |

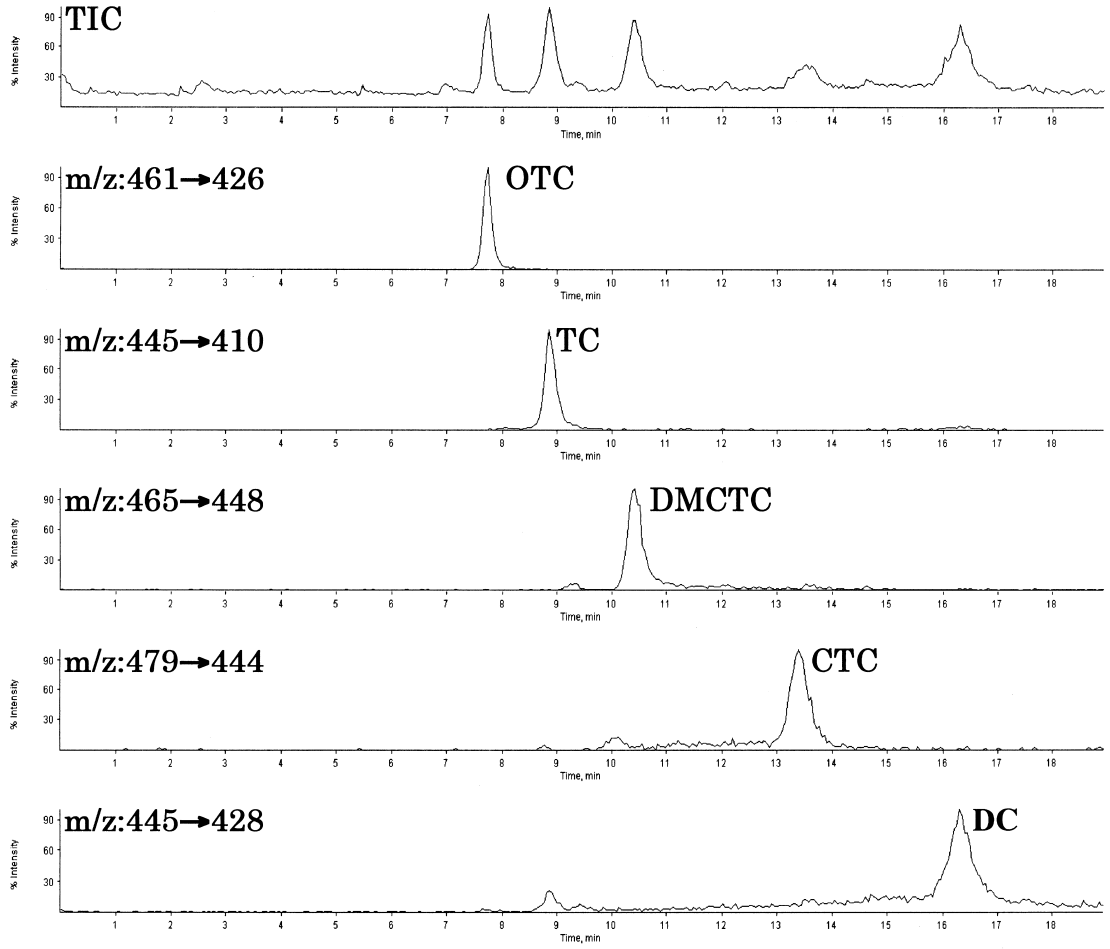



Fig. 2. Total ion chromatogram and SRM profiles of standard tetracyclines under APCI LC–MS–MS conditions.

OTC, 8.8 min for TC, 10.4 min for DMCTC, 13.5 min for CTC, and 16.2 min for DC, respectively. Tandem mass spectra of each TC taken at the top of each peak on the TIC are shown in Fig. 3. All of the TCs gave $[M+H-NH_3]^+$ and $[M+H-NH_3-H_2O]^+$ as product ions, except for DC. Six standard solutions containing TCs between 0.05 and 5 μg/ml (each solution contains DMCTC at a concentration of 5 μg/ml as an internal standard) were prepared and 10 μl were injected into the APCI LC–MS–MS system. Calibration curves (six points) were constructed by peak-area ratios of TCs to DMCTC calculated from SRM profiles. Good linearity was observed ($r=0.995$) for all of the TCs. Limits of detection (LODs) were calculated by a signal-to-noise ratio of 3:1; these limits were 5 pg/μl for OTC and TC, 20 pg/μl for CTC, and 10 pg/μl for DC.

### *3.2. Recovery of TCs in foods*

After adding TCs to swine muscle at a concentration of 0.1 ppm, the TCs were extracted and cleaned up by solid-phase extraction as described in Section 2.2, and the sample solutions were analysed by APCI LC–MS–MS under the optimal conditions described in Section 3.1. TIC and SRM profiles are shown in Fig. 4. Although some interfering peaks from the sample were observed in TIC, each of the TC peaks is clearly observed in SRM profiles, indicating that we can determine TCs in swine

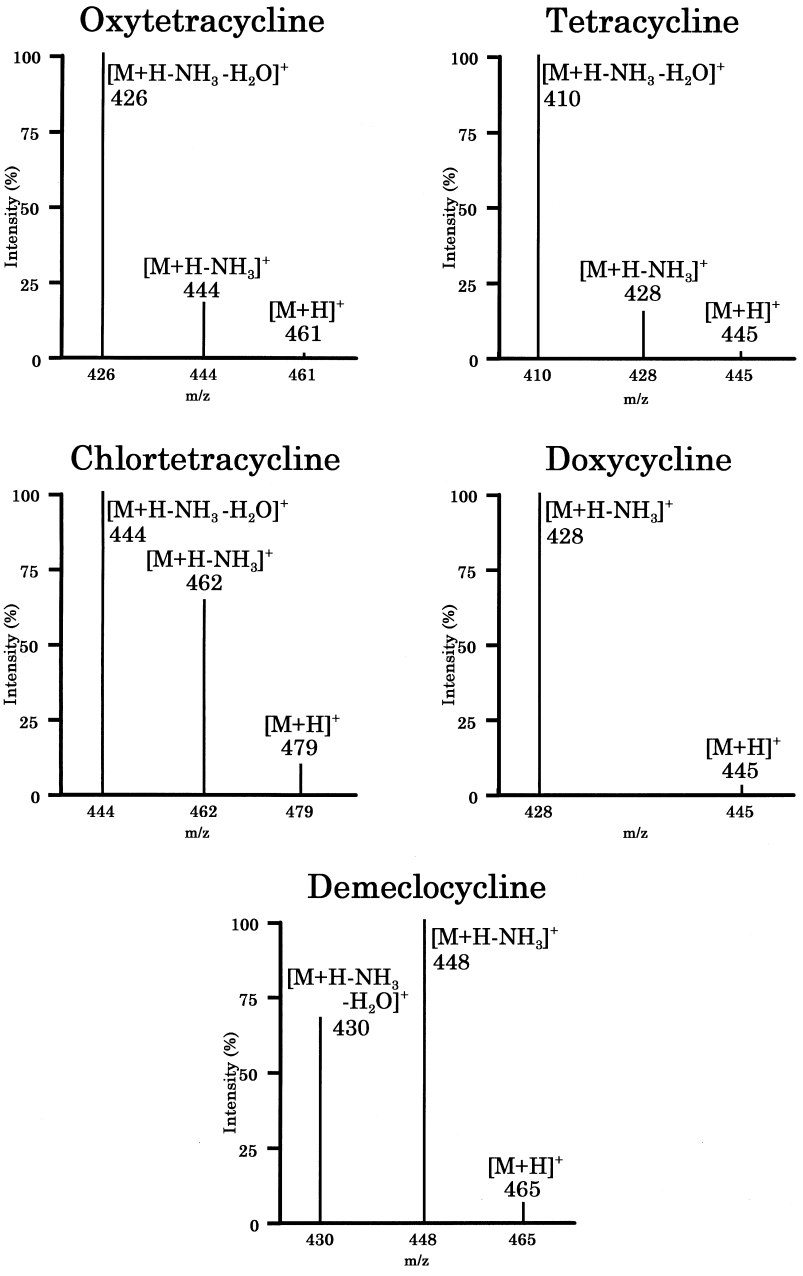



Fig. 3. APCI tandem mass spectra of standard tetracyclines under APCI LC–MS–MS conditions.

muscle using these SRM profiles. Furthermore, the tandem mass spectra of each TC are the same as standards shown in Fig. 3. Therefore, we can also confirm TCs in swine muscle.

As described above, we considered that the use of an internal standard is essential for determining TCs using APCI LC–MS–MS, so we selected DMCTC as an internal standard. To show the effect of DMCTC as an internal standard, we list the recoveries and relative standard deviations (RSD) of

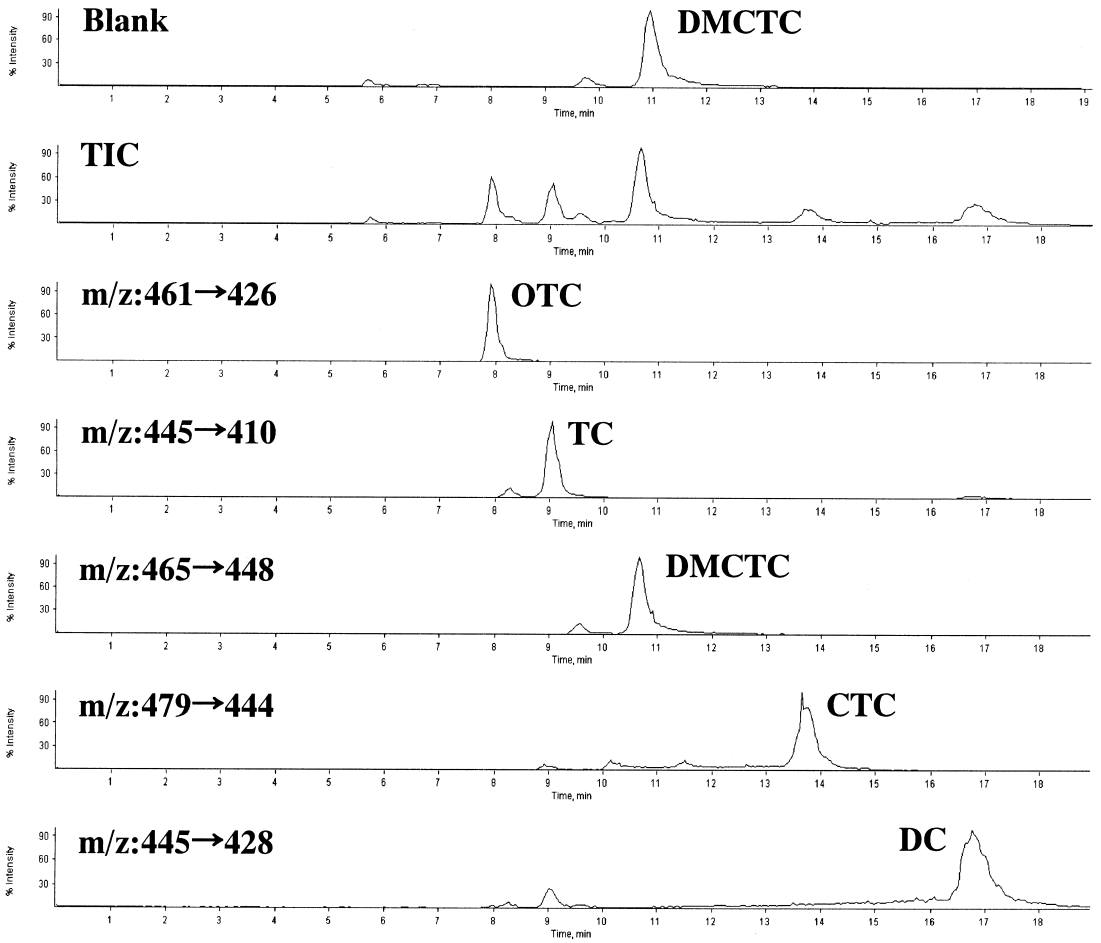



Fig. 4. Total ion chromatogram and SRM profiles of TCs fortified at 0.1 ppm in swine muscle under APCI LC–MS–MS conditions.

TCs from swine muscle fortified at 0.05, 0.10, and 0.50 ppm in Table 2. When DMCTC was not used as an internal standard, the recoveries ranged from 96.5 to 183.3% and RSD varied from 6.0 to 39.1%. On the other hand, when DMCTC was used as an internal standard, good recoveries (67.2–81.6%) and

Table 2
Effect of DMCTC as an internal standard on recoveries of TCs from swine muscle[a]

| | Added (ppm) | Recovery (RSD)% | | | |
|---|---|---|---|---|---|
| | | OTC | TC | CTC | DC |
| Without I.S. | 0.05 | 183.3(33.1) | 179.7(33.8) | 161.9(39.1) | 166.7(35.5) |
| | 0.10 | 134.0(17.7) | 131.6(16.4) | 120.6(16.3) | 116.3(18.0) |
| | 0.50 | 115.4(6.0) | 106.2(7.2) | 96.5(8.2) | 105.3(12.6) |
| With I.S. | 0.05 | 80.0(7.7) | 78.8(7.6) | 69.5(8.7) | 71.5(4.3) |
| | 0.10 | 81.6(1.9) | 80.0(2.8) | 73.6(2.1) | 70.8(3.8) |
| | 0.50 | 80.4(3.9) | 74.0(6.1) | 67.2(1.9) | 71.9(4.2) |

[a] $n=5$.

Table 3
Recovery of TCs from fortified bovine and swine tissues[a]

| Added (ppm) | Sample | | Recovery (RSD)% | | | |
|---|---|---|---|---|---|---|
| | | | OTC | TC | CTC | DC |
| 0.05 | Bovine | Liver | 60.5(4.3) | 71.8(2.9) | 64.9(6.0) | 60.1(4.3) |
| | | Kidney | 69.7(5.6) | 67.1(3.3) | 65.7(2.6) | 63.9(5.5) |
| | | Muscle | 67.3(2.5) | 74.3(3.8) | 63.2(2.9) | 71.8(5.5) |
| | Swine | Liver | 66.6(3.7) | 67.7(2.9) | 63.1(7.2) | 62.1(4.5) |
| | | Kidney | 80.3(1.2) | 77.1(4.6) | 78.3(4.7) | 70.5(4.9) |
| | | Muscle | 80.0(7.7) | 78.8(7.6) | 69.5(8.7) | 71.5(4.3) |
| 0.10 | Bovine | Liver | 69.6(2.7) | 74.3(2.9) | 72.4(7.5) | 62.3(1.6) |
| | | Kidney | 71.2(2.6) | 72.0(2.9) | 69.8(3.0) | 72.2(4.6) |
| | | Muscle | 64.3(3.4) | 72.7(3.5) | 71.5(1.9) | 63.2(4.1) |
| | Swine | Liver | 70.5(4.0) | 73.4(3.1) | 79.2(3.0) | 64.9(2.3) |
| | | Kidney | 72.2(5.6) | 80.5(4.8) | 78.9(4.0) | 68.1(6.3) |
| | | Muscle | 81.6(1.9) | 80.0(2.8) | 73.6(2.1) | 70.8(3.8) |
| 0.50 | Bovine | Liver | 66.4(3.1) | 77.9(3.3) | 71.6(5.2) | 63.4(3.9) |
| | | Kidney | 77.6(4.3) | 78.3(3.0) | 70.1(2.6) | 66.8(3.4) |
| | | Muscle | 82.6(7.1) | 80.6(6.0) | 72.6(4.0) | 69.0(4.5) |
| | Swine | Liver | 72.7(5.2) | 78.0(1.9) | 75.0(3.2) | 69.8(5.1) |
| | | Kidney | 73.6(4.0) | 78.3(3.0) | 70.1(2.6) | 66.8(3.4) |
| | | Muscle | 80.4(3.9) | 74.0(6.1) | 67.2(1.9) | 71.9(4.2) |

[a] $n=5$.

Table 4
Recovery of TCs from fortified chicken, fish, egg, milk, and honey[a]

| Added (ppm) | Sample | | Recovery (RSD)% | | | |
|---|---|---|---|---|---|---|
| | | | OTC | TC | CTC | DC |
| 0.05 | Chicken | Liver | 81.6(2.6) | 81.3(4.9) | 77.8(3.3) | 79.8(4.8) |
| | | Muscle | 71.9(7.7) | 77.9(3.4) | 71.4(4.8) | 81.4(3.0) |
| | Yellowtail | | 73.4(7.2) | 68.6(8.4) | 73.7(8.2) | 74.3(4.6) |
| | Eel | | 81.1(3.7) | 83.6(2.7) | 81.5(5.4) | 69.6(3.0) |
| | Egg | | 76.0(6.7) | 69.6(7.6) | 61.3(8.0) | 67.1(7.6) |
| | Milk | | 79.8(6.2) | 67.7(6.2) | 65.6(4.3) | 61.9(6.9) |
| | Honey | | 77.1(3.1) | 70.9(4.4) | 64.2(5.3) | 66.6(6.8) |
| 0.10 | Chicken | Liver | 80.4(2.1) | 79.5(4.7) | 77.2(4.5) | 78.7(6.1) |
| | | Muscle | 81.1(5.2) | 78.5(5.4) | 68.5(4.8) | 73.7(3.6) |
| | Yellowtail | | 76.9(5.1) | 66.8(3.1) | 79.4(2.9) | 67.6(3.2) |
| | Eel | | 79.2(4.1) | 78.8(3.6) | 77.1(2.2) | 77.0(3.8) |
| | Egg | | 81.1(4.1) | 74.2(3.4) | 63.7(3.8) | 63.6(5.8) |
| | Milk | | 74.1(3.8) | 75.5(4.4) | 81.2(3.0) | 76.9(4.5) |
| | Honey | | 80.7(2.5) | 70.6(5.5) | 66.6(3.1) | 70.9(5.4) |
| 0.50 | Chicken | Liver | 74.3(1.6) | 76.8(3.6) | 81.0(1.6) | 79.4(4.2) |
| | | Muscle | 82.3(4.8) | 81.5(3.3) | 80.6(4.3) | 83.2(4.8) |
| | Yellowtail | | 75.5(4.3) | 78.0(6.2) | 71.1(6.7) | 68.2(7.4) |
| | Eel | | 74.6(2.1) | 70.3(2.6) | 85.1(4.0) | 78.0(1.9) |
| | Egg | | 85.5(7.8) | 87.0(2.5) | 88.9(1.4) | 73.8(5.9) |
| | Milk | | 81.5(2.9) | 75.0(4.1) | 66.6(3.6) | 69.9(3.6) |
| | Honey | | 82.1(1.6) | 79.2(4.2) | 76.1(2.4) | 74.0(3.8) |

[a] $n=5$.

RSD (1.9–8.7%) were obtained. In APCI LC–MS, the efficiency of ionization of the target compounds is strongly influenced by the co-eluting substances from LC, because the co-eluting substances change the reagent ion composition in chemical ionization process. Therefore, we consider that these high

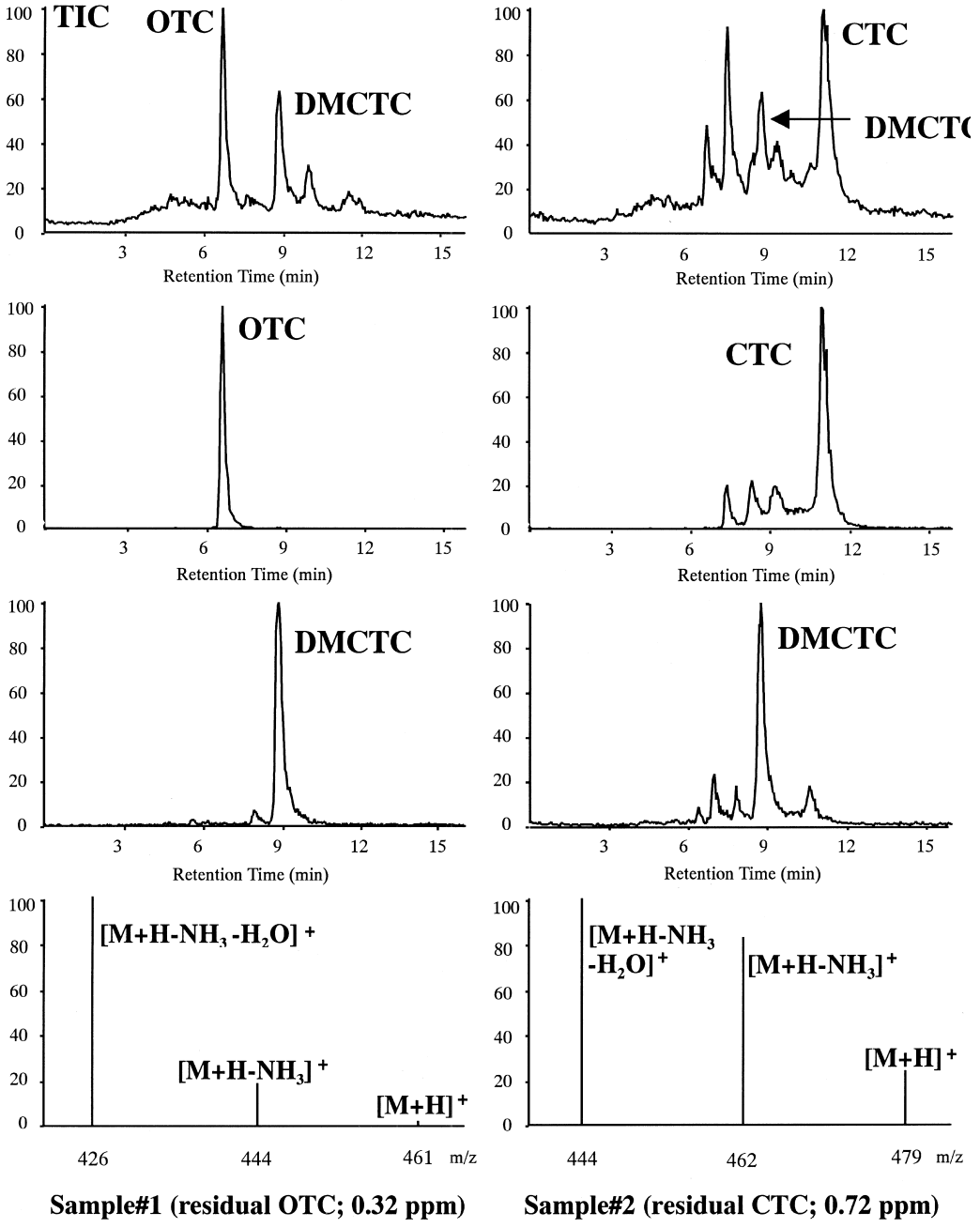



Fig. 5. Total ion chromatogram and SRM profiles of residual oxytetracycline (sample #1) and chlortetracycline (sample #2) in swine kidneys under APCI LC–MS–MS conditions.

recoveries and RSD are caused by this influence. Because of the correction of ionization efficiency by an internal standard, these results suggested that the present APCI LC–MS–MS method with DMCTC as an internal standard could be applied to various foods.

Various food samples including bovine, swine, chicken, yellowtail, eel, eggs, and milk fortified with TCs at concentrations of 0.05, 0.1, and 0.5 ppm were analysed by the present APCI LC–MS–MS methods. The recoveries and RSD are shown in Tables 3 and 4. The overall recoveries for various foods ranged from 60.1 to 88.9% and RSD ranged from 1.2 to 8.7%. The detection limits were 0.001 ppm for OTC and TC, 0.004 ppm for CTC, and 0.002 ppm for DC. These values mean that the present method, including extraction, clean up, and APCI LC–MS–MS, provides sufficient recoveries with good repeatability for determining TCs in foods.

To evaluate the capability of the present method, we analysed swine kidney samples that had previously been shown to contain residual TCs by microbiological assay. As a result, we found that sample #1 contained OTC at a concentration of 0.32 ppm and sample #2 contained CTC at a concentration of 0.72 ppm (Fig. 5). In addition, we were able to confirm residual OTC in sample #1 and CTC in sample #2 by the tandem mass spectra of each TC taken at the top of each peak on the SRM chromatograms, as shown in Fig. 5 (bottom). These results indicate that the present method can be applied to an actual sample in the market.

## 4. Conclusion

Although ESI LC–MS–MS cannot be used to determine residual TCs in foods, we were able to establish a suitable technique using APCI LC–MS–MS. All of the TCs examined, except DC, gave $[M+H-NH_3]^+$ and $[M+H-NH_3-H_2O]^+$ as the product ions, when $[M+H]^+$ was selected as the precursor ion. By setting the nebulizer probe temperature to 475°C, we were able to use a mobile phase containing oxalic acid without clogging problems at the APCI interface, since oxalic acid decomposes to carbon dioxide and water at high temperature. DMCTC was very effective as an internal standard for determining TCs in various foods. The recovery of TCs from various foods including animal tissues, honey, milk, eggs, and fish fortified at levels of 0.05, 0.10, and 0.50 ppm was 60.1–88.9% with an RSD of 1.2–8.7%. The detection limits were 0.001 ppm for OTC and TC, 0.004 ppm for CTC, and 0.002 ppm for DC. The present method was successfully used to determine TCs in swine kidney samples that had been previously found by microbiological assay.

## Acknowledgements

This work was supported by the Ministry of Education, Science, Sports, and Culture of Japan.

## References

[1] H. Oka, Y. Ikai, N. Kawamura, J. Hayakawa, J. Assoc. Off. Anal. Chem. 74 (1991) 894.
[2] H. Oka, Y. Ikai, J. Hayakawa et al., J. Food Hyg. Soc. Japan 36 (1995) 759.
[3] J. Van der Greef, C.J.M. Arts, M. Van Baak, E.R. Verheij, in: Proceedings of the Euro Residue II Conference, 1993, pp. 35–40.
[4] K.-I. Harada, M. Suzuki, H. Oka, Chromatography and mass spectrometry for analysis of natural products, in: T. Matsuo, R.M. Caprioli, M.L. Gross, Y. Seyama (Eds.), Biological Mass Spectrometry, John Wiley, Chichester, 1994, pp. 606–630, Ch. 317.
[5] J. Keever, R.D. Voyksner, K.L. Tyczkowska, J. Chromatogr. A 794 (1998) 57.
[6] R. Straub, M. Linder, R.D. Voyksner, Anal. Chem. 66 (1994) 3651.
[7] H. Oka, Y. Ikai, J. Ito et al., J. Chromatogr. B 693 (1997) 337.
[8] H. Oka, H. Matsumoto, K. Uno, K. Harada, S. Kadowaki, M. Suzuki, J. Chromatogr. 325 (1985) 265.
[9] P.J. Kijak, M.G. Leadbetter, M.H. Thomas, E.A. Thompson, Biomed. Mass Spectrom. 20 (1991) 789.
[10] G.B. Kenion, G.T. Carter, J. Ashraf, M.M. Siegel, D.B. Border, Quantitative analysis of pharmaceuticals by thermospray liquid chromatography/mass spectrometry, in, in: Liq. Chromatogr./Mass Spectrom., ACS Symp. Ser.420, ACS, 1990, pp. 140–165, Ch. 9.
[11] W.J. Blanchflower, R.J. McCracken, A.S. Haggan, G. Kennedy, J. Chromatogr. B 693 (1997) 351.