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Short communication

Determination of phenylethanolamine A in animal hair, tissues and feeds by reversed phase liquid chromatography tandem mass spectrometry with QuEChERS

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ABSTRACT

A simple, sensitive and reliable analytical method was developed for the determination of a new beta-agonist phenylethanolamine A in animal hair, tissues and animal feeds by ultra high performance liquid chromatography–positive electrospray ionization tandem mass spectrometry (UHPLC–ESI-MS/MS) with QuEChERS. Samples were extracted with acetonitrile/water (80:20, v/v). The extract was purified through QuEChERS method, then was dried with nitrogen and residues were redissolved in mobile phase for hair sample or directly diluted with 0.1% formic acid in water for other samples, and analyzed by LC–MS/MS on a Waters Acquity BEH C_{18} column with 0.1% formic acid in water/methanol as mobile phase with gradient elution. The samples were quantified using phenylethanolamine A-D_3 as internal standards. The proposed method was validated according to the European Commission Decision 2002/657/EC determining specificity, decision limit (CCα), detection capability (CCβ), recovery, precision, linearity, robustness and stability. The CCα values ranged from 0.10 to 0.26 μg/kg. The CCβ values ranged from 0.20 to 0.37 μg/kg. The mean recoveries of 95.4–108.9% with intra-day CVs of 2.2–5.6% and inter-day CVs of 3.1–6.2% were obtained. The method is demonstrated to be suitable for the determination of phenylethanolamine A in animal hair, tissues and animal feeds. The total time required for the analysis of one sample except animal hair sample, including sample preparation, was about 25 min.

1. Introduction

Beta-agonists are originally used in the therapeutic treatment of asthma and preterm labor in humans [1]. However, these compounds are also misused as growth promoters in livestock by diverting nutrients from fat deposition to the production of muscle tissues in animals [2]. This misuse had caused some severe accidental poisonings in humans [3,4]. Therefore, all beta-agonists are banned as feed additives for growth promotion in animals in China and EU [5,6]. With the crackdown of banned beta-agonists, such as clenbuterol, salbutamol and ractopamine, a new beta-agonist named phenylethanolamine A has been illegally used in livestock in China (Fig. 1) [7]. In order to control the use of phenylethanolamine A, specific and sensitive methods for identifying and quantifying of phenylethanolamine A in animal hair, tissues and animal feeds are required.

Although gas chromatography–mass spectrometry (GC–MS) [8–11] and liquid chromatography–mass spectrometry (LC–MS) [12–17] methods have been developed to identify beta-agonists in biological samples, there are little literatures on identification of phenylethanolamine A in animal tissues and feeds [7,18]. A LC–MS/MS method had been recently developed by Sun and Yan in swine muscle [7]. However, the pre-treatment procedure of the method was very complicated and time-consuming because the combination of enzymatic hydrolysis, liquid–liquid extraction and solid phase extraction (SPE) were used to cleanup. Therefore, rapid, specific and sensitive methods for the identification and quantification of phenylethanolamine A in hair, animal tissues and feeds are required.

The QuEChERS method was previously used by Anastassiades et al. for the determination of pesticides in fruit and vegetable samples with primary and secondary amine (PSA) as the base sorbent [19]. The method has already received worldwide acceptance because of the simplicity and high throughput enabled a laboratory to process significantly a large number of samples in a given time. Moreover, the method had recently been used for the determination of veterinary drug residue and mycotoxins [20,21]. Due to high efficiency of QuEChERS, it is necessary to develop QuEChERS method for phenylethanolamine A in animal hair, tissues and feeds.

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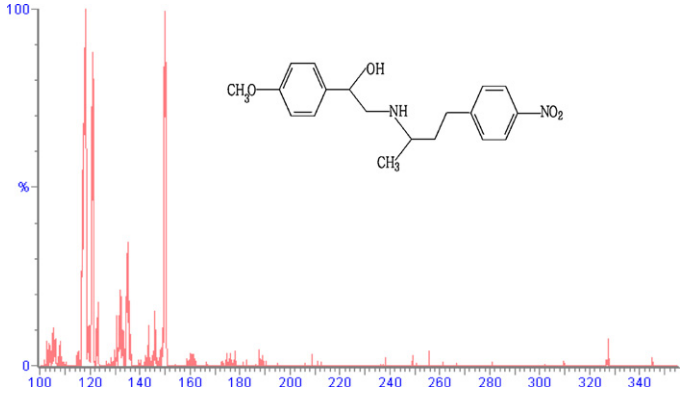

Fig. 1. Mass spectrum of phenylethanolamine A at 30 eV and its structure.

Here we developed a simple and reliable confirmatory LC–MS/MS analytical method for analyzing phenylethanolamine A in animal hair, tissues and feeds with QuEChERS cleanup procedure. Validation parameters tested were specificity, CCα, CCβ, recovery, precision, linearity, robustness and stability.

2. Materials and methods

2.1. Materials and reagents

Methanol, acetonitrile and formic acid were LC grade. Hexane was analytical grade. Phenylethanolamine A was purchased from Dr. Ehrenstorfer (Augsburg, Germany). Phenylethanolamine A-D_3 was purchased from WITEGA Laboratorien Berlin-Adlershof GmbH (Berlin, Germany). Sodium chloride, anhydrous magnesium sulphate, hydrochloric acid and sodium hydroxide were obtained from Sinopharm Chemical Reagent Co., Ltd. (Shanghai, PR China). PSA sorbent was purchased from Agilent Technologies Inc. (Santa Clara, CA, USA). The water was purified with a Milli-Q reverse osmosis system (Millipore, Milford, MA, USA).

2.2. Standard solutions

Stock solutions of phenylethanolamine A and phenylethanolamine A-D_3 (100 μg/mL) were prepared in methanol. Three fortifying standard solutions (25, 37.5 and 50 ng/mL) were prepared by diluting stock standard solution with acetonitrile. Two internal working standard solutions of phenylethanolamine A-D_3 (50 and 500 μg/L) were prepared in acetonitrile. Six working standard solutions (0.025–2.5 μg/L) of phenylethanolamine A were prepared by diluting stock solution with 0.1% formic acid in water/methanol (80:20, v/v). Two individual working standard solutions (1000 μg/L) for MS–MS optimization were prepared by diluting stock solutions with 0.1% formic acid in water/methanol (80:20, v/v).

2.3. Chromatographic conditions

A Waters Acquity UPLC instrument (Milford, MA, USA) was used in the present experiment. Separation was carried out on an Acquity BEH C_{18} column (100 mm × 2.1 mm, 1.7 μm) maintained at 30 °C. The mobile phase consisted of solvent A (0.1% formic acid in water) and solvent B (methanol). Initial gradient conditions were set to 20% B and held for 0.5 min before incorporating a linear gradient increasing to 80% B at 2.5 min and held for 1.0 min. At 3.6 min the gradient was programmed to initial conditions to reequilibrate the column for 1.4 min (total run time 5 min). The flow rate was 0.30 mL/min. The injection volume was 10 μL in full loop injection mode.

2.4. Mass spectrometry conditions

Detection was carried out by a Waters Xevo^{TM} TQ triple-quadrupole MS fitted with electrospray ionization (ESI) probe operated in the positive ion mode. The following parameters were optimal: capillary voltage, 3000 V; ion source temperature, 150 °C; desolvation gas temperature, 500 °C; desolvation gas flow rate, 1000 L/h. Detection was carried out in multiple reaction monitoring (MRM) mode. Argon was used as the collision gas, and the collision cell pressure was 4 mbar. The selected MRM transitions for phenylethanolamine A were m/z 345.3 > 117.8 and 345.3 > 150.0 with a dwell time of 0.25 s. The transition chosen for quantification was 345.3 > 150.0. The selected MRM transition for phenylethanolamine A-D_3 was 348.3 > 153.1 with a dwell time of 0.25 s. The cone voltage was 20 V. As for the collision energy, it was 30 eV for m/z 345.3 > 117.8, 22 eV for m/z 345.3 > 150.0 and m/z 348.3 > 153.1.

2.5. Sample preparation

2.5.1. Animal tissues and feeds

A 5 g of homogenous representative sample was weighed in a 50 mL plastic centrifuge tube and 100 μL of internal standard solution at 500 μg/L was added. Then vortexed for 15 s and allowed to stand at room temperature for 30 min. After addition of 25 mL of acetonitrile/water (80:20, v/v), the sample was homogenized by a high-speed blender (Ultra-Tyrrax T25; IKA, Germany) for 1 min. After addition of 2.0 g of NaCl and 10 mL of hexane (5 mL of water were added for feed samples), the mixture was shaken vigorously for 1 min. To separate aqueous and organic phase, the sample was centrifuged at 5000 rpm for 3 min. An aliquot of middle organic phase (2 mL) was transferred to a 5 mL centrifuge tube with 150 mg anhydrous $MgSO_4$ and 50 mg PSA. After shaking vigorously on vortex for 1 min, the tube was centrifuged at 10,000 rpm for 2 min. The purified extract was diluted with 0.1% formic acid in water in 4:6 (0.40 mL purified extract mixed with 0.60 mL of 0.1% formic acid in water) ratio. Prior to final instrumental analysis, sample solution was passed through the 0.20 μm filter.

2.5.2. Animal hair

Hair (500 mg), which had been cut into small pieces shorter than 1 mm with scissors, was incubated overnight at 45 °C in 5 mL 0.1 M HCl after addition of 100 μL of internal standard solution at 50 μg/L. After cooling, the mixture was adjusted pH to 7.0 with 0.5 M NaOH. Then, 20 mL of acetonitrile/water (80:20, v/v) was added. The sample was homogenized by a high-speed blender (Ultra-Tyrrax T25; IKA, Germany) for 1 min. The following cleanup steps were identical to Section 2.5.1. After purification, the purified extract (1.5 mL) was evaporated to dryness in a water bath at 40 °C under nitrogen and reconstituted in 500 μL of 0.1% formic acid in water/methanol (80:20, v/v). Prior to final instrumental analysis, sample solution was passed through the 0.20 μm filter.

2.6. Method validation

The evaluation of the suitability of the method for the determination of phenylethanolamine A in swine hair, swine tissues, chicken mixed feed and swine mixed feed was carried out according to the European Commission Decision 2002/657/EC [22].

To verify the absence of interfering substances around the retention time of phenylethanolamine A, 20 blank samples for each kind of sample were analyzed.

The linearity of the method was determined by assaying each calibration standard at six concentration levels (0.025, 0.05, 0.1, 0.25, 1.0 and 2.5 μg/L) over the linear range of phenylethanolamine A. The concentration of internal standard was 1.0 μg/L. Linear

regression analysis of calibration standard data was performed by plotting the peak area ratio of quantitative ion pair of phenylethanolamine A to internal standard.

The CCα was established by analyzing 20 blank materials per matrix to be able to calculate the signal to noise ratio at the time window in which the analyte is expected. Three times the signal to noise ratio (qualitative ion pair) was used as CCα. The CCβ was established by analyzing 21 blank materials per matrix fortified with phenylethanolamine A at 0.50 μg/kg.

Recovery of phenylethanolamine A was measured in blank samples that were fortified at 0.50 μg/kg, 0.75 μg/kg and 1.0 μg/kg. The fortified samples were analyzed and the recoveries were calculated by comparing the measured concentrations to the fortified concentrations. The repeatability was measured on the 21 fortified blank samples ($n = 7$ replicates per concentration level and analyzed in three independent analytical runs) for each kind of sample and expressed by coefficient of variation (inter-day CVs). The within-laboratory reproducibility was measured on the 21 fortified blank samples ($n = 7$ replicates at 0.50 μg/kg fortification level and analyzed at three occasions with three different operators) for each kind of sample and expressed by coefficient of variation (CV_R).

Robustness first was established by introducing changes in volume of extract solution (15, 20, 25 and 30 mL) for fortified liver samples at 0.50 μg/kg. Then, robustness was evaluated by introducing small changes in the chromatographic system, like flow rate (0.25, 0.30 and 0.35 mL/min), column temperature (25, 30, 35 and 40 °C) and the concentration of formic acid in solvent A (0.05, 0.10 and 0.15%). Robustness of chromatographic system change was assessed by injecting the same matrix (liver) fortified standard solution (2.0 μg/L) six times under each above chromatographic condition.

The stability was determined in two different ways: (a) in solvent (stock solutions) and (b) in matrix (fortified level was 0.50 μg/kg, each kind of matrix was fortified 15 samples).

3. Results and discussion

3.1. LC–MS/MS optimization

Working solutions of 1000 μg/L were infused to optimize the MS–MS parameters of phenylethanolamine A and phenylethanolamine A-D_3 and to select the appropriate diagnostic ions. The infusion process was carried out with the same chromatographic conditions as those used during analysis. The ESI^+ was selected due to its sensitivity, ruggedness and easy handling and maintenance.

Because beta-agonists belong to group A of Annex I, Council Directive 96/23/EC [23], a minimum of four identification points are required, which were obtained by monitoring one parent ion (1 point) and two transitions (each 1.5 points). The selected transitions for phenylethanolamine A and the optimal MS–MS conditions are described in Section 2.4.

After optimization of MS parameters, mobile phase composition had been investigated. We had found the sensitivity of phenylethanolamine-A can be significantly enhanced by adding small amounts of formic acid in mobile phase. There was no significant difference between two mobile phases (0.1% formic acid in water/acetonitrile and 0.1% formic acid in water/methanol) in sensitivity. In order to protect column, the gradient elution system with 0.1% formic acid in water/methanol had been chosen to analyze phenylethanolamine-A.

3.2. Sample preparation

To develop a simple pretreatment procedure, we decided to enhance the selectivity of extraction by means of QuEChERS employing partitioning of acetonitrile/water mixture induce by addition of inorganic salts. While the analytes are transferred into an organic phase, some more polar matrix impurities are left in aqueous layer. Moreover, hexane was added to remove fat.

After centrifugation, the middle phase of the extract was directly diluted with 0.1% formic acid in water and injected to LC–MS/MS without PSA purification for animal tissues and feeds. However, there were about 20–35% and 25–45% ion suppression at 2:8 and 4:6 dilution ratio, respectively. To decrease the matrix effect, the matrix effects (signal suppression/enhancement, SSE) were evaluated by comparing of external matrix matched calibration slope with the external solvent calibration slope in range 0.025–2.5 μg/L at 4:6 dilution ratio after PSA purification for animal tissues and feeds and 3-fold concentration factor after PSA purification for animal hair (Fig. 2). The results revealed that the matrix effect of phenylethanolamine A was decreased with the increase of the amount of PSA from 0 mg to 50 mg and no significant difference between 50 mg and 100 mg. So, 50 mg of PSA was used in the present study.

A suitable deconjugation step is required for simultaneous determination of beta-agonists in animal tissues and urine. However, the main form is free state in animal tissues and urine for aniline-type beta-agonist including phenylethanolamine A [24].

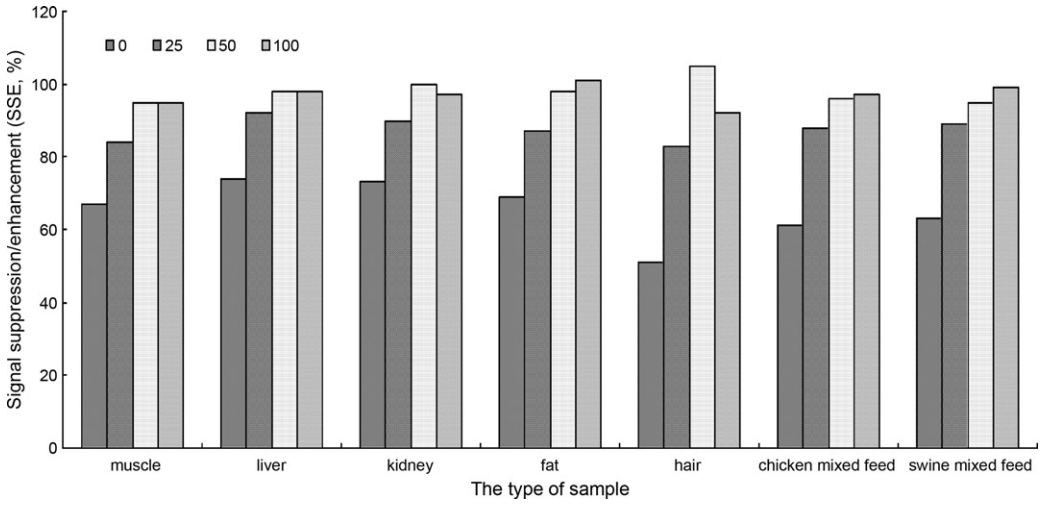

Fig. 2. The effect of different PSA amounts on the matrix effect at 4:6 dilution ratio after PSA purification.

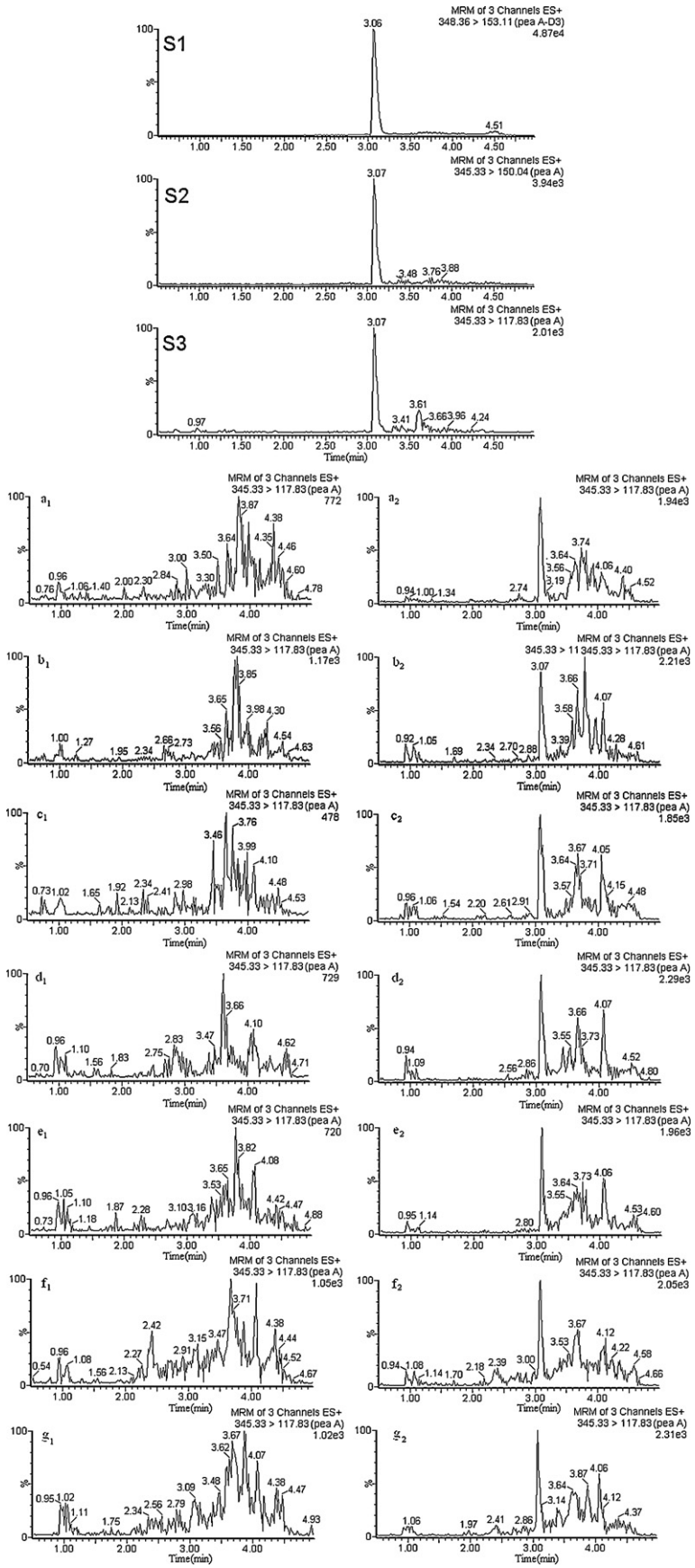

Fig. 3. The MRM chromatogram of phenylethanolamine (0.05 μg/L, S_2 and S_3) and phenylethanolamine-D_3 (1.0 μg/L, S_1) in standard solution and the MRM chromatograms of blank and fortified samples at the 0.50 μg/kg level for phenylethanolamine in muscle (a), liver (b), kidney (c), fat (d), hair (e), chicken mixed feed (f) and swine mixed feed (g).

Table 1
Mean recoveries of phenylethanolamine A from animal hair, tissues and animal feeds by LC–MS/MS.

Type of sample	Fortified concentration (μg/kg)	Intra-day mean recovery and CVs (%, $n=7$)			Inter-day mean recovery and CVs (%, $n=21$)	CV_R (%)
Muscle	0.50	98.3(4.3)	101.3(5.5)	96.7(4.2)	98.8(4.9)	5.1
	0.75	98.7(2.2)	99.2(2.5)	97.9(4.4)	98.6(3.1)	–
	1.0	99.7(2.7)	99.0(3.2)	101.7(4.3)	100.1(3.5)	–
Liver	0.50	95.4(5.0)	97.5(3.0)	103.7(5.5)	98.9(5.7)	5.8
	0.75	96.0(3.9)	103.1(3.5)	96.2(2.3)	98.4(4.7)	–
	1.0	97.6(4.3)	103.3(4.4)	97.6(2.9)	99.5(4.7)	–
Kidney	0.50	104.4(4.5)	102.0(3.9)	99.7(4.9)	102.0(4.6)	7.1
	0.75	97.0(3.8)	103.1(5.4)	99.0(4.7)	99.7(5.2)	–
	1.0	98.4(3.5)	97.2(4.6)	99.3(3.3)	98.3(4.2)	–
Fat	0.50	104.2(4.7)	97.4(3.6)	102.1(4.1)	101.2(5.3)	5.1
	0.75	97.5(3.4)	105.4(5.0)	98.9(3.2)	100.6(6.2)	–
	1.0	101.3(4.5)	97.8(3.1)	98.4(3.7)	99.2(4.3)	–
Hair	0.50	96.4(4.9)	102.4(3.3)	99.1(4.1)	99.3(4.6)	6.3
	0.75	100.5(4.2)	96.5(4.0)	96.8(3.6)	97.9(5.0)	–
	1.0	97.8(4.0)	100.7(3.2)	98.5(2.9)	99.0(4.8)	–
Chicken feed	0.50	96.3(4.7)	95.8(3.8)	99.8(4.1)	97.3(5.1)	6.8
	0.75	106.2(3.8)	97.2(3.3)	98.6(4.0)	100.7(5.3)	–
	1.0	98.5(4.2)	96.6(3.8)	98.1(3.5)	97.7(4.4)	–
Swine feed	0.50	98.8(5.1)	103.6(3.2)	108.9(4.7)	103.8(6.2)	6.6
	0.75	97.4(3.9)	105.1(4.4)	96.4(4.2)	99.6(5.8)	–
	1.0	95.9(4.0)	99.4(5.6)	97.0(3.5)	97.4(5.2)	–

Hooijerink et al. had found the conjugated rate was about only 5% for clenbuterol in urine samples [25]. Moreover, a positive muscle sample from Henan Institute of Veterinary Drug Control was analyzed using the method and another method developed by Sun and Yan with enzymatic hydrolysis [7]. The result was 5.89 ± 0.17 μg/kg ($n=3$) for our method with external quantification and higher than the concentration (5.52 ± 0.33 ($n=3$)) analyzed by the another method. So, enzymatic hydrolysis had not been used in the present study.

For the determination of β_2-agonists residue in biological sample, the pretreatment of developed methods usually include buffer solution extraction, enzymatic hydrolysis and SPE procedure [11–13,16]. Consequently, at least 2–3 h (sometimes over 18 h) must be required for determination of one sample. Compared with the conventional pretreatment procedures, the established QuEChERS pretreatment procedure was very simple and economic. It can meet the requirements of rapid increase in the number of samples.

3.3. Method validation

3.3.1. Linearity

The calibration graph was obtained by plotting the peak area of quantitative ion pair of phenylethanolamine A to internal standard at 0.025–2.5 μg/L. The linear equation was $Y = 1.3827X + 0.0108$ with the correlation coefficient (R^2) of 0.9993. The maximum individual residual deviate was 5.8% at all of standard points. Using the curve, recoveries can be calculated at each fortification level. The MRM chromatograms of standard solution are shown in Fig. 3.

3.3.2. Specificity

The specificity was evaluated by analyzing 20 blank samples for each kind of sample. Fig. 3 indicates that there were no interfering peaks from endogenous compounds at the retention time of phenylethanolamine A.

3.3.3. Recovery and precision

Based on the level recommended by the EU-CRL for other aniline-type beta-agonists (26), a level of 0.50 μg/kg of phenylethanolamine A was chosen as the target analytical level. And, three different fortified concentrations (0.50, 0.75 and 1.0 μg/kg) had been chosen according to the European Commission Decision 2002/657/EC [22]. The results are summarized in Table 1. The mean recoveries, intra-day CVs, inter-day CVs and within-reproducibility (CV_R) varied from 95.4 to 108.9%, from 2.2 to 5.6%, from 3.1 to 6.2% and from 5.1 to 7.1%, respectively.

3.3.4. CCα and CCβ

According to the concept of the European Commission Decision 2002/657/EC, three times of the signal to noise ratio (qualitative ion pair) was used for CCα. The CCβ was established by analyzing 21 blank materials per matrix fortified with phenylethanolamine A at 0.50 μg/kg (Fig. 3). The value of the decision limit (CCα) plus 1.64 times the standard deviation of the within-laboratory reproducibility of the measured content equals the detection capability (CCβ). Results are presented in Table 2. The results of the CCα ranged from 0.10 to 0.26 μg/kg. The CCβ values ranged from 0.20 to 0.37 μg/kg. Additionally, limit of detection (LOD) was 0.13 μg/kg after a 10-fold dilution for swine muscle sample. The LOD is better than the previously published LC–MS/MS method for phenylethanolamine A in swine muscle (0.20 μg/kg) even if a 10-fold concentration had been used [7].

3.3.5. Robustness

After robustness experiment on volume change of extract solution for fortified liver sample at 0.50 μg/kg, it was found that the mean recoveries ($n=7$) were 106.2, 97.5, 103.7, and 104.1% for 15, 20, 25, 30 mL of extract solution, respectively. There were not significant differences for these recoveries. The possible reason was the use of isotope compound as internal standard for quantification in the present study.

Table 2
CCα and CCβ (μg/kg) obtained for phenylethanolamine A in animal hair, tissues and animal feeds by LC–MS/MS.

Matrix	Muscle	Liver	Kidney	Fat	Hair	Chicken mixed feed	Swine mixed feed
CCα	0.13	0.12	0.10	0.12	0.11	0.23	0.26
CCβ	0.21	0.22	0.22	0.20	0.21	0.34	0.37

The Waters Xevo^{TM} TQ MS is a robust platform for quantitative LC–MS/MS. Compared with conventional LC–MS/MS, much more MRM transitions can be acquired with higher sensitivity in a single analysis, especially combined with ultra high performance LC systems.

The analytical results of the matrix fortified standard solution (2.0 μg/L) were quantified with an external standard solution (2.0 μg/L) analyzed in the same chromatographic condition. The concentrations of the matrix standard solution were 1.90–2.01 μg/L for phenylethanolamine A. The CVs ranged from 0.52% to 1.89%. These results demonstrate that changes of chromatographic conditions did not significantly influence the analytical results.

3.3.6. Stability

The stock standard solutions in methanol were stored for at least one month at −20 °C. The stock solutions were analyzed every week by UPLC and the instrumental responses were compared with the peak areas obtained at the moment of solution preparation ($t = 0$). The acceptance criterion was a response comprised between 95% and 105% of the initial one [26]. Fortified samples at 0.50 μg/kg stored at −20 °C were analyzed after 3, 7 and 14 days. It was found that the recoveries of phenylethanolamine A had no obvious change.

3.4. Applications of the method

Forty samples (twenty swine muscle and twenty swine liver sample) commercially available from the local market were analyzed for phenylethanolamine A using the above method. No residue was found in these samples.

4. Conclusion

In the present study, a fast and sensitive method was developed for the determination of phenylethanolamine A in seven kinds of matrixes (hair, muscle, liver, kidney, fat, chicken mixed feed and swine mixed feed) by LC–MS/MS with QuEChERS. This method was validated with fortified blank samples and satisfactory recoveries were obtained. The CCα and CCβ were found to be sufficiently low to determine the residue of phenylethanolamine A in animal hair, tissues and animal feeds.

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