การตรวจวัดบิสฟีนอลเอไดไกลซิดิลอีเธอร์ บิสฟีนอลเอฟไดไกลซิดิลอีเธอร์ โนโวแลคไกลซิดิลอีเธอร์และอนุพันธ์ในปลากระป๋องโดยเทคนิคแมทริกซ์โซลิดดิสเพอร์ชันและอัลตราไฮเพอร์ฟอร์แมนซ์ลิควิด โครมาโทกราฟี-แทนเดมแมสสเปกโทรเมตรี

Simultaneous determination of bisphenol A diglycidyl ether, bisphenol F diglycidyl ether, novolac glycidyl ether and their derivatives in canned fishes by matrix solid dispersion with ultra high performance liquid chromatography-tandem mass spectrometry

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บทคัดย่อ

งานวิจัยนี้ได้พัฒนาการตรวจวัดปริมาณสารมอนอเมอร์ทั้งหมด 13 ชนิด ได้แก่ บิสฟีนอลเอไดไกลซิดิลอีเธอร์ (BADGE) บิสฟีนอลเอฟไดไกลซิดิลอีเธอร์ (BFDGE) โนโวแลคไกลซิดิลอีเธอร์ (NOGE 3-6 ring) และอนุพันธ์ (BADGE·H$_2$O, BADGE·2H$_2$O, BADGE·HCl, BADGE·2HCl, BADGE·H$_2$O·HCl, BFDGE·2H$_2$O and BFDGE·2HCl) ในอาหารกระป๋อง โดยใช้เทคนิคลิควิดโครมาโทกราฟี-แทนเดมแมสสเปกโทรเมตรี (LC-MS/MS) และแมทริกซ์โซลิดดิสเพอร์ชันที่รู้จักในชื่อว่า QuEChERS ทั้งนี้ได้ศึกษาและตรวจสอบความใช้ได้เพื่อให้ได้วิธีที่มีความน่าเชื่อถือสำหรับตรวจวัดปริมาณ โดยการตรวจสอบความใช้ได้ของวิธีดำเนินการตาม Eurachem Guide: 2014 โดยเติมสารละลายมาตรฐานที่ความเข้มข้น 5 ระดับ (0.025, 0.50, 1.00, 9.00 และ 18.0 มิลลิกรัมต่อกิโลกรัม) ค่าร้อยละกลับคืนมีค่าอยู่ในช่วง 60.8 ถึง 114.2% ที่ 0.025 มิลลิกรัมต่อกิโลกรัม, 81.2 ถึง 109.3% ที่ 0.50 มิลลิกรัมต่อกิโลกรัม, 80.1 ถึง 109.2% ที่ 1.00 มิลลิกรัมต่อกิโลกรัม, 83.7 ถึง 110.0% ที่ 9.00 มิลลิกรัมต่อกิโลกรัม และ 84.6 ถึง 109.1% ที่ 18.0 มิลลิกรัมต่อกิโลกรัมและได้ค่าการทำซ้ำที่ดี (ร้อยละส่วนเบี่ยงเบนมาตรฐานประมาณ 1.13 ถึง 19.5) โดยมีค่าขีดจำกัดของการตรวจพบเท่ากับ 0.010 มิลลิกรัมต่อกิโลกรัมสำหรับมอนอเมอร์แต่ละชนิด และขีดจำกัดของการหาปริมาณมีค่าเท่ากันสำหรับทุกชนิด เท่ากับ 0.025 มิลลิกรัมต่อกิโลกรัม กราฟมาตรฐานมีความเป็นเส้นตรงสูงถึง 1000 ไมโครกรัมต่อลิตรด้วยค่าสัมประสิทธิ์การกำหนดที่ดี (r^2) อยู่ในช่วงระหว่าง 0.9983 ถึง 0.9999

Abstract

A method was successfully developed for the simultaneous determination of thirteen monomers, *i.e.* bisphenol A diglycidyl ether (BADGE), bisphenol F diglycidyl ether (BFDGE), novolac glycidyl ether (NOGE 3-6 ring) and their derivatives (BADGE·H$_2$O, BADGE·2H$_2$O, BADGE·HCl, BADGE·2HCl, BADGE·H$_2$O·HCl, BFDGE·2H$_2$O and BFDGE·2HCl) in canned foods. Liquid chromatography with tandem mass spectrometry (LC-MS/MS) and matrix solid dispersion method known as QuEChERS were investigated and validated to obtain a reliable method for the application of concentration measurement. The method validation was performed according to Eurachem Guide: 2014 using fortified samples at five different concentration levels (0.025, 0.50, 1.00, 9.00 and 18.0 mg kg^{-1}). The extraction recoveries ranged from 60.8 to 114.2% at 0.025 mg kg^{-1}, 81.2 to 109.3% at 0.50 mg kg^{-1}, 80.1 to 109.2% at 1.00 mg kg^{-1}, 83.7 to 110.0% at 9.00 mg kg^{-1} and 84.6 to 109.1% at 18.0 mg kg^{-1} with good repeatability (%RSD $\approx$ 1.13-19.5). The limits of detection were 0.010 mg kg^{-1} for all monomers, while the limits of quantitation were the same at 0.025 mg kg^{-1} for all analytes. The calibration curves were provided linear up to 1000 μg L^{-1} with the excellent coefficient of determination (r^2) in the range 0.9983-0.9999.

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คำสำคัญ : บิสฟีนอลเอไดไกลซิดิลอีเธอร์ บิสฟีนอลเอฟไดไกลซิดิลอีเธอร์ โนโวแลคไกลซิดิลอีเธอร์ อัลตราไฮเพอร์ฟอร์แมนซ์ลิควิด โครมาโทกราฟี-แทนเดมแมสสเปกโทรเมตรี เมทริกซ์โซลิดดิสเพอร์ชัน อาหารกระป๋อง

Keywords : Bisphenol A diglycidyl ether, Bisphenol F diglycidyl ether, Novolac glycidyl ether, Ultra-high-performance liquid chromatography-tandem mass spectrometry, Matrix solid dispersion, Canned fish, QuEChERS

1. Introduction

Food safety is increasingly concerned about public human health that affects food production worldwide [1, 2]. Food contaminants occur from raw materials and packaging involving in every step of production. Food contact materials (FCMs) are widely used for food manufacturing and a potential source of toxic substances migrating into foods. Therefore FCMs, *i.e.* metal cans have been controlled to prevent and avoid risks to health problems. Even though interior can coatings will deter interaction between food components and metals, they may release chemical substances, *e.g.* bisphenol A diglycidyl ether (BADGE), bisphenol F diglycidyl ether (BFDGE) and novolac glycidyl ether (NOGE) into foodstuffs when the coating would not be produced in good quality. It must not be only a poor quality coating, but also the characteristics of the foodstuff (pH, acid, base) can cause the monomers to migrate out of the coating. Moreover, during storage these monomers can migrate and react with food contents, *i.e.* water and hydrochloric acid to form hydrolyzed and chlorinated products such as $BADGE{\cdot}H_2O$, $BADGE{\cdot}2H_2O$, BADGE·HCl, BADGE·2HCl, $BADGE{\cdot}H_2O{\cdot}HCl$, $BFDGE{\cdot}2H_2O$ and BFDGE·2HCl [3]. These low molecular weight compounds (< 1 000 Da) are absorbed in the gastrointestinal tract and suspected to harm to human health. Although recent available data of BADGE and hydrolyzed products are compiled with a lack of carcinogenicity and genotoxicity, the data of chlorinated products are not available on genotoxicity. However, BADGE and derivatives have been recently revealed the cytotoxicity in human placental cells and show an effect on placental lipids and CYP19 activity. Since the researchers have found that the accumulation in blood [4] and food sensitization in young children [5], BADGEs and bisphenol analogs would be a raised concern for human exposure. Therefore, the EU Commission restricts the use of these compounds. According to EC No. 1895/2005 [6], the sum of BADGE and hydrolyzed products shall not excess 9 mg kg^{-1} food or food simulants. The sum of chlorinated products shall not exceed 1 mg kg^{-1} food or food simulants. NOGE and BFDGE shall not allow use in food contact materials. For law enforcement, the analytical method which plays an important role consist of sample preparation and measurement steps. The reliable techniques are required to fulfill this need [7].

The food simulants have been applied for the safety assessments of these compounds contaminated in foods; therefore, early research focused on the extraction of BADGE and its derivatives into the water, ethanol, acetic acid, and oil as migration testing [8-10]. The determination of these compounds in real foods will be a better representative of risk assessments to human health; although it requires multiple steps and complicated analytical methods as revealed in many previous publications of researches [3, 11-17]. The HPLC-FLD provided a very low detection limit at 0.01-4.20 ng g^{-1} owing to good sensitivity with a fluorescent detector, but it still limited only BADGE, BFDGE and their derivatives [18, 19]. However, NOGE also involved in the safety issue of can coating. In another research, ultrasound-assisted solvent extraction of porous membrane-packed sample and LC-MS/MS was published and obtained good recoveries and low

LOQ of 0.8-1.5 ng g^{-1} in canned vegetables [20]. Although several researches showed very low detectable LOD and LOQ, these techniques such as membrane required longer time for equilibrium that would be a critical point of sample preparation and lead to an error [20]. The matrix-matched calibration was applied that would cause more complicate and re-create several calibrations to match with different kinds of matrix [21]. Nowadays, the standard methods of these compounds are published in 2 methods as following BS EN 15136: 2006 for BADGE, BFDGE and their derivatives and BS EN 15137: 2006 for NOGE and its derivatives. These standard methods provide accurate results, but they have the deficit of using simple HPLC techniques and run times of 85 min per injection. Liquid chromatography coupled with tandem mass spectrometry (LC–MS/MS) has been applied to gain the advantages of shorter run time and simultaneous method for all analytes. The sample preparation step is also important for measurement. The matrix solid dispersion or QuEChERS (Quick, Easy, Cheap, Effective, Rugged and Safe) method has become popular and is widely applied as a sample preparation technique for pesticide determination in fruits and vegetables [22]. This technique was investigated and revealed to seek out the sample preparation method which obtains less labor, time and solvent consumption for LC-MS/MS technique [23].

This study aimed to investigate and validate fast sample preparation and simultaneous method for determination of BADGE, BFDGE, NOGE and their derivatives, as well as the benefit of confidential technique with good accuracy and precision. Moreover, the developed method would be proved and met the requirement of ISO/IEC 17025: 2017.

2. Experimental methods

2.1 Materials and reagents

Magnesium sulfate anhydrous ($MgSO_4$), sodium phosphate monobasic ($NaH_2PO_4•H_2O$ or NaPhosphate), sodium acetate anhydrous (CH_3COONa or NaOAc), tri-sodium citrate dihydrate ($C_6H_5Na_3O_7•2H_2O$ or NaCitrate), ammonium acetate (CH_3COONH_4 or NH_4OAc), di-ammonium hydrogen citrate ($C_6H_8O_7•2NH_3$ or NH_4Citrate), and sodium chloride (NaCl), analytical grade, were purchased from Merck (Darmstadt, Germany) as well as formic acid for the pH adjustment of buffer solution as mobile phase (MP). Ammonium formate was supplied by Sigma-Aldrich (Buchs, Switzerland) for MP preparation. Methanol and acetonitrile, gradient grade for liquid chromatography, was also supplied by Merck. HPLC water was obtained from a Milli-Q water system (Millipore, Billerica, MA, USA) at 18.2 MΩ•cm. Octadecylsilane (C18) was purchased from Waters (Milford, MA, USA), as well as a 0.2 μm polytetrafluoroethylene (PTFE) syringe filter.

Nitrogen (purity ~ 95.0-99.5%) was supplied by Agilent nitrogen generator (USA) for an electrospray ionization source (ESI). Ultra-high-purity nitrogen (N_2) was purchased from Lab Solution and Engineering Co., Ltd. (Nonthaburi, Thailand) for a collision-induced gas (CID gas).

2.2 Standards

Bisphenol A diglycidyl ether (BADGE, CAS No. 1675-54-3, ≥95%), bisphenol A (2,3-dihydroxypropyl) glycidyl ether ($BADGE·H_2O$, CAS No. 76002-91-0, ≥95%), bisphenol A bis(2,3-dihydroxypropyl) ether ($BADGE·2H_2O$, CAS No. 5581-32-8, ≥97%), bisphenol A (3-chloro-2-hydroxypropyl) glycidyl ether (BADGE·HCl, CAS No. 13836-48-1, ≥90%), bisphenol A bis(3-chloro-2-hydroxypropyl) ether

(BADGE·2HCl, CAS No. 4809-35-2, ≥97%), bisphenol A (3-chloro-2-hydroxypropyl) (2,3-dihydroxypropyl) ether (BADGE·H_2O·HCl, CAS No. 227947-06-0, ≥95%), bisphenol F diglycidyl ether (BFDGE, CAS No. 2095-03-6), bisphenol F bis(2,3-dihydroxypropyl) ether (BFDGE·$2H_2O$, CAS No. 72406-26-9, ≥95%), bisphenol F bis(3-chloro-2-hydroxypropyl) ether (BFDGE·2HCl, Product No. 15139, ≥90%), novolac glycidyl ether (3-Ring NOGE mixtures of isomers, CAS No. 158163-01-0, ≥90%), (4-Ring NOGE mixtures of isomers, chain-like or branched, Product No. 04976, ≥90%), (5-Ring NOGE mixtures of isomers, chain-like or branched, Product No. 12109, ≥90%) and (6-Ring NOGE mixtures of isomers, chain-like or branched, Product No. 30977, ≥80%) were purchased from Sigma-Aldrich (Buchs, Switzerland).

2.3 Instrumentation and LC-MS/MS conditions

The LC-MS/MS system consisted of an Agilent Technologies 1290 Infinity LC separation module and an Agilent Technologies 6460 Triple Quad LC/MS System. The column was a Zorbax Eclipse Plus-C18 (2.1 × 50 mm; 1.8 μm) with a Zorbax Eclipse Plus-C18 (2.1 × 12.5 mm; 1.8 μm) as a guard-column (Agilent Technologies) operated at 40 °C. The injection volume was 3 μL. Elution conditions were developed to successfully determine all analytes in simultaneous method [23]. Methanol and 25 mM of ammonium formate at pH 3 were applied as mobile phase with gradient elution at a flow rate of 0.4 mL min^{-1}. The gradient condition was shown in below:

Table 1. LC gradient condition

Time (min)	25 mM Ammonium formate (pH 3) (%)	Methanol (%)
0	55	45
1	50	50
3	30	70
9	10	90
9.5	0	100
10	55	45
12	55	45

The LC system was coupled with a triple quadrupole MS system equipped with an electrospray ionization source (ESI) in positive mode. Nitrogen was used as a sheath and collision gas. The ESI conditions were set as follows: gas temperature at 320 °C, gas flow at 8 L min^{-1}, nebulizer at 45 psi, sheath gas heater at 350 °C, sheath gas flow at 11 L min^{-1} and capillary at 4000 V. The scan segments for each compound and ammonium adducts $[M+NH_4]^+$ used as precursor ions are shown in Table 2.

Table 2. Optimized conditions of mass spectrometry for determination of BADGE, BFDGE, NOGE and derivatives.

Compound Name	Precursor Ion	Product Ion 1	Product Ion 2	Dwell	Fragment (V)	Collision Energy (V)	Cell Accelerator (V)
BADGE	358.2	191.1	135.1	30	100	9	4
BADGE•2HCl	430.2	227.0	135.0	30	100	6	4
BADGE•H_2O•HCl	412.3	227.0	135.0	30	100	9	4
BADGE•HCl	394.2	227.0	135.0	30	100	6	4
BADGE•$2H_2O$	394.2	209.2	135.1	30	108	12	4
BADGE•H_2O	376.2	209.2	135.1	30	108	8	4
BFDGE	330.2	163.2	133.0	30	100	8	4
BFDGE•2HCl	403.3	386.3	198.8	30	100	4	4
BFDGE•$2H_2O$	366.4	349.2	181.1	30	80	4	4
NOGE 3 ring	492.2	325.3	145.0	30	110	8	4
NOGE 4 ring	654.3	163.2	106.9	30	140	23	4
NOGE 5 ring	816.3	325.0	162.8	30	160	25	4
NOGE 6 ring	978.0	162.9	107.0	30	216	36	4

2.4 Samples

Tuna samples were fully uncanned, pre-cooked and selected to minimize the contamination of BADGE, BFDGE, NOGE and their derivatives from the coating of metal can. The tuna was homogenized and mixed with some ingredients, *i.e.* water, salt and oil to obtain the tuna in oil matrix. The ratio of added ingredients was the same as sold in local markets in Thailand. The tuna samples were prepared by adding pre-cooked tuna (75%), deionized water (9.78%), salt (0.5%) and sunflower oil (14.7%). For the study of extraction conditions, the tuna samples were fortified at 0.50 mg kg^{-1} and analyzed in triplicate. For method validation, the tuna samples were fortified at five levels (0.025, 0.50, 1.00, 9.00 and 18.0 mg kg^{-1}) in ten replicates per each concentration level including blank sample with no additional standard.

2.5 Sample preparation as matrix solid dispersion or QuEChERS method

The sample extraction was performed following the modified QuEChERS method [23]. The homogenized tuna samples in matrices were prepared by using a DIAX 900 (Heidolph, Schwabach, Germany). A sub-sample of 10 ± 0.01 g was weighed into a 50 mL centrifuge tube and added 10 mL of acetonitrile to extract for 1 min. The sample was added with 1 ± 0.05 g of NaCl and 4 ± 0.20 g of $MgSO_4$ and then vigorously shaken for 1 min. The mixture was centrifuged using a Biofuge Stratos (Heraeus Instruments, Newtown, CT, USA) for 5 min at 3000 rpm. Two mL of acetonitrile solution was transferred and shaken with the mixture of 50 mg C18 and 300 mg $MgSO_4$ for 30 sec. To separate the sorbents, the mixture was centrifuged again for 5 min at 3000 rpm. The extracted solution was filtered before injection to LC-MS/MS system.

2.6 Correction factors of matrix effect

Since mass spectrometry have been faced the problem of matrix interferences, matrix effect was investigated through the standard addition method [24-26]. Analytes were spiked in the sample with none-interested compound before extraction, therefore matrix effects contributed to mass response. This experiment is applied to compensate any signal and interference error during the measurement step due to the lack of isotope-labeled internal standard. The correction factor (MEF) was calculated from the ratio of standard | concentration in the matrix sample and pure standard. The equation is as following:

$$\mathrm{MEF} = \frac{C_M}{C_P} \qquad (1)$$

where C_M and C_P are the concentrations of standards in matrix samples and pure standards, respectively.

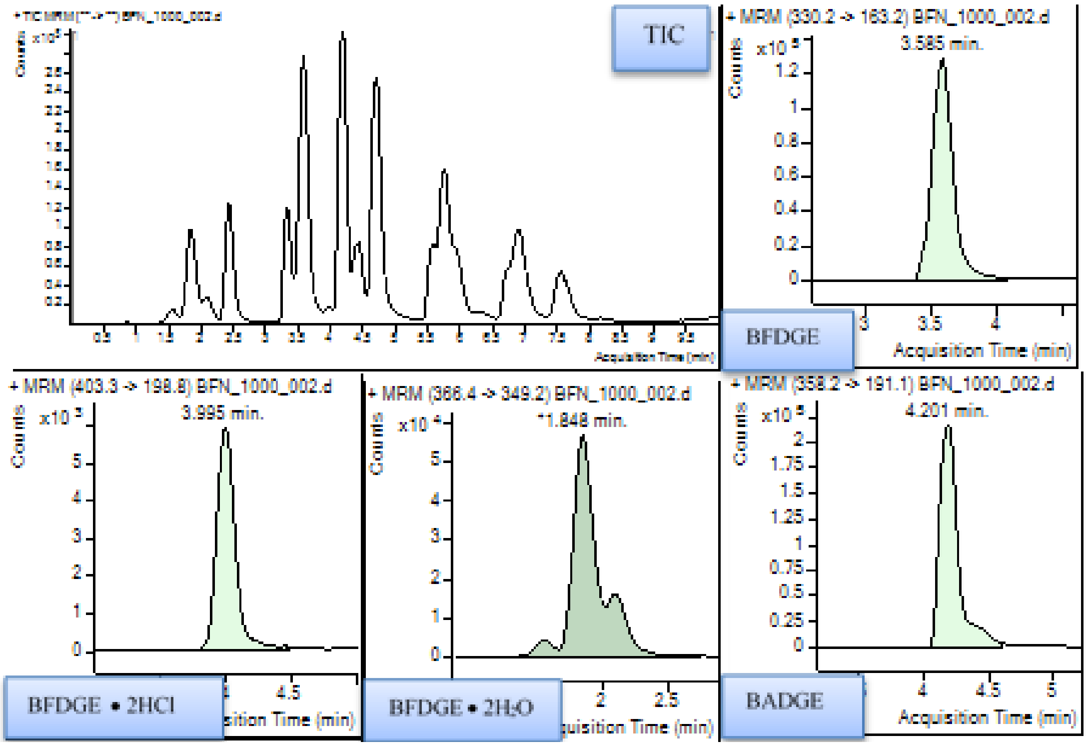
2.7 Calibration curves

The 500 mg L^{-1} of standard solutions for BADGE, BFDGE and their derivatives were individually prepared in acetonitrile and stored at -20 °C as well as the 1000 mg L^{-1} for NOGE and its derivatives. At this storage temperature provided high stability according to the study of Szczepańska et al [27]. The stock solutions were diluted by acetonitrile to obtain six concentration levels of 10, 25, 50, 100, 500 and 1000 μg L^{-1}. All calibration solutions were daily prepared and linearity was investigated in triplicate analysis.

3. Results and discussion

3.1 Optimization of LC-MS/MS conditions

The LC-MS/MS was evaluated to obtain a fast and simultaneous method for determination of BADGE, BFDGE, NOGE and their derivatives. The scan segments and source parameters were optimized to gain best sensitivity for measurement. In previous study, several kinds, compositions and flow rates of mobile phase were investigated; for example, acetic acid-sodium acetate at pH 3, formic acid-water at pH 3, formic acid-ammonium formate at pH 3, methanol and acetonitrile as well as injection volume [23]. As a result the use of methanol and ammonium formate provided the best signal. Additionally the concentrations (10, 25, 40 and 55 mM) and pH (3.00, 3.50, 3.75 and 4.00) of ammonium formate were also studied and the best condition was 25 mM and pH 3 [23]. In varied pH, the peak area provided two time higher at pH 3.00 but the lower signal obtained at the highest pH 4.00. In acid condition, these compounds could form hydronium, sodium and ammonium adducts, but these required the sufficiency of sodium and ammonium ions from the buffer solutions. The different concentrations of ammonium formate were also investigated and found that only peak areas were slightly changed with variation of 10 to 55 mM and peak shapes were similar for all conditions. The ammonium adducts of these compounds provided the best signal; therefore, in this study, the 25 mM ammonium formate at pH 3: methanol was selected because of the highest responses in electrospray. This mobile phase condition was applied in this study; moreover, these results had the same trends with previous publication [17]. The extracted-ion chromatogram of 1000 μg L^{-1} mix-standard solution was developed by using optimized condition as illustrated in Figure 1. In the chromatogram, some peaks of analytes were not fully separated due to varied isomers of each compound [28, 29]. The injection volume has related to ratio of water and organic solvent for the dilution of extracted sample. When higher volume of water was applied, the larger injection volume could be used. However, in this study, the sensitivities of all analytes were satisfied with a 3 μL injection volume and acetonitrile used. This condition provided the benefits of less analysis time from the additional step of sample preparation, solvent consumption and no need of additional instrument for evaporation to reconstitute into other solvents, *e.g.* methanol:water (1:1) or acetonitrile: water (1:1) etc.



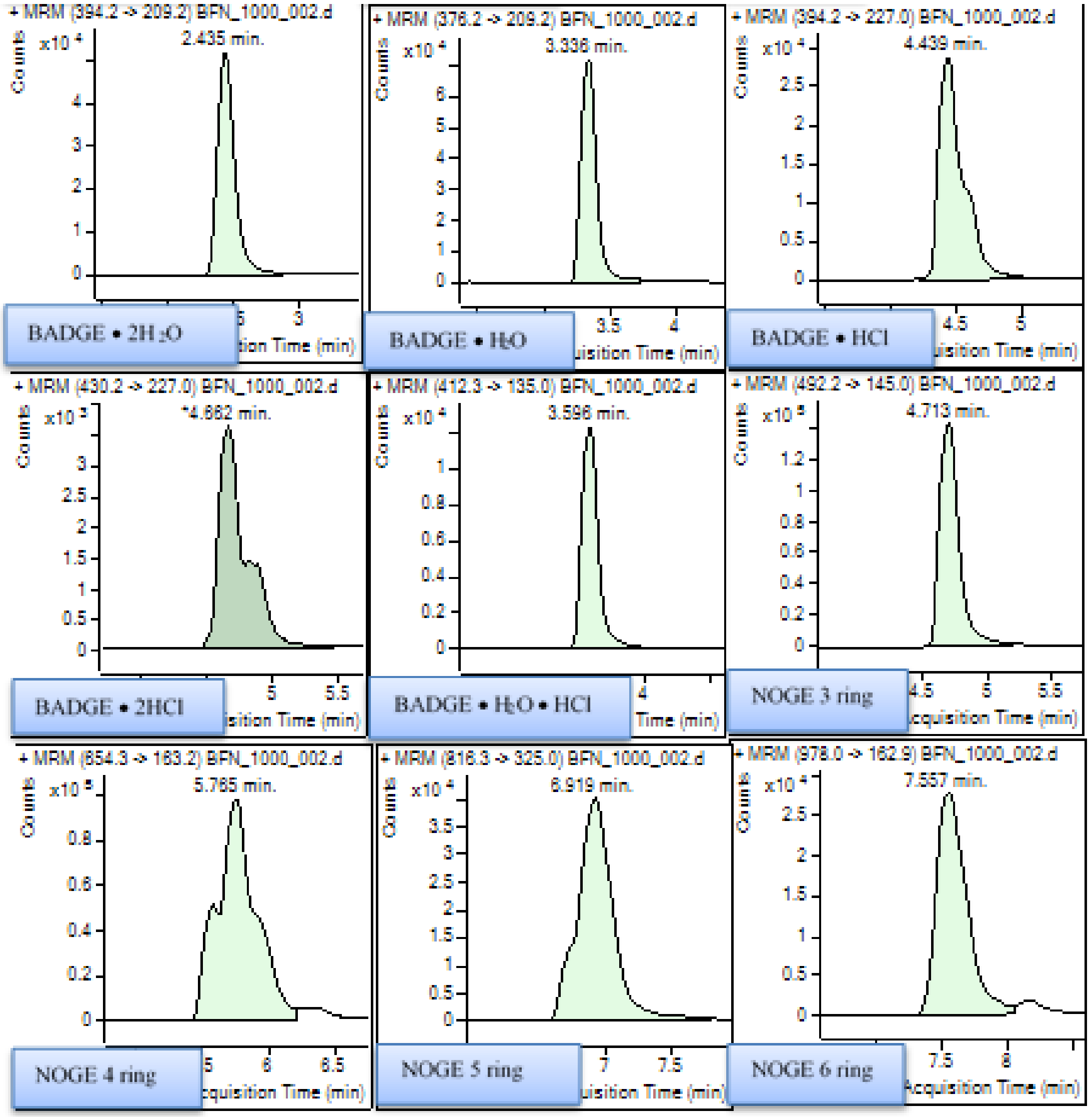


Figure 1 : The total ion chromatogram (TIC) and extracted-ion chromatogram of 1000 $\mu g\ L^{-1}$ mixed standard solution (BADGE, BFDGE, NOGE and their derivatives): BADGE, BFDGE, NOGE, BADGE·H_2O, BADGE·$2H_2O$, BADGE·HCl, BADGE·2HCl, BADGE·H_2O·HCl, BFDGE·$2H_2O$, BFDGE·2HCl, NOGE 3 ring, NOGE 4 ring, NOGE 5 ring, NOGE 6 ring.

3.2 Optimization of extraction conditions

The previous study was investigated QuEChERS method by varying inducers and sorbents in order to obtain successful phase separations, minimized interferences and also provide good accuracy and precision [23]. Each inducer, i.e. NaPhosphate, NaOAc, NaCitrate, NH_4OAc and NH_4 Citrate, was added to replace NaCl after extraction with acetonitrile; due to different pH and water absorption, the triplicated average of recoveries were also different for each inducer. The use of NaCl, NaOAc, NH_4OAc and NH_4Citrate gave the percentages of recoveries in the acceptable range (81.1 to 112.2%) for all analytes, while NaCitrate and NaPhosphate provided relatively low recoveries for NOGE 6 ring (65.3% for NaCitrate and 59.4% for NaPhosphate). Therefore, NaCl was selected because of low cost and safety. Each sorbent, i.e. PSA, C18, combination of PSA and C18, was studied because their properties could absorb fat and oil for C18 and amino acid for PSA; therefore, they were applied during the cleanup step to reduce co-extraction [30, 31]. However, the use of C18 and the combination of PSA and C18 showed non-significant difference using two-tailed t-test at a 95% confidence level; hence, only C18 was used as sorbent for method validation.

3.3 Matrix effect

Matrix effect was investigated through the standard addition method. Analytes were spiked in the sample before extraction, hence both recovery and matrix effects contributed to mass response. The tuna samples were selected to be the representative of canned fishes, since there is large consumption in Thailand. The responses were compared between pure standard calibrations and matrix-matched calibrations, using a two-tailed t-test at a 95% confidence level. These results indicated significant differences ($P < 0.05$) for all compounds; therefore, the correction of matrix effect was required to compensate for the difference of detector responses between pure standards and matrix samples from food components, e.g. protein, fat and water content etc. The ratio of matrix effect (MEF) was applied to compensate any errors during measurement steps such as ionization efficiency in the liquid phase and gas phase. The higher inferences would affect to the formation of evaporation in gas phase and reduce ionization efficiency; hence, it provided low response in detector and also cause the false negative of ion suppression. Since the previous study was required to use the standard addition technique for calculating the amount of analytes, MEF ratio with the pure standard calibration was employed to solve this problem and also gain accurate, precise, while less work with the correction factor and with that a great optimization of the sample throughput.

3.4 Method validation

The performances of this developed method were revealed in relation to linearity, accuracy, precision, instrument detection limit (IDL), limit of detection (LOD) and limit of quantification (LOQ). The sample blanks were analyzed in ten replicates to investigate contaminants from itself and determine the LOD and LOQ. The linear regression of six calibration levels were studied using relationships between analytes’ concentrations and peak areas, as shown in Table 3. The coefficients of determination (r^2) were better than 0.9983 for all compounds; hence, good linearities were obtained from 25 to 1 000 $\mu g\ L^{-1}$. Accuracy and precision were performed at five concentration levels (0.025, 0.50, 1.00, 9.00 and 18.0 $mg\ kg^{-1}$, as considering at a regulation limit and two times) and ten replicates per level. Accuracy was expressed as recoveries and ranged from 60.8 to 114.2% at 0.025 mg kg^{-1}, 81.2 to 109.3% at 0.50 mg kg^{-1}, 80.1 to 109.2% at 1.00 mg kg^{-1}, 83.7 to 110.0% at 9.00 mg kg^{-1} and 84.6 to 109.1% at 18.0 mg kg^{-1} for all monomers. The details were shown in Table 4. Precision was expressed as relative standard deviation (RSD), and ranged from 5.07 to 23.1% at 0.025 mg kg^{-1}, 4.07 to 9.74% at 0.50 mg kg^{-1}, 1.62 to 8.57% at 1.00 mg kg^{-1}, 4.59 to 10.7% at 9.00 mg kg^{-1} and 3.69 to 9.36% at 18.0 mg kg^{-1} for all analytes. All recoveries and RSDs were in the acceptable ranges. The LOD and LOQ were calculated from three and ten times of the standard deviation of results at 0.025 mg kg^{-1} (near zero concentration as mentioned in Eurachem Guide) [32]. The IDL was investigated by using pure standards that were injected into LC-MS/MS and obtained low detection limit at part-per-billion (ppb) level. All performance details were shown in Table 3 and 4.

Table 3. Analytical method performance for thirteen monomers, i.e. BADGE, BFDGE, NOGE and their derivatives.

Analyte	Coefficient of determination (r^2)	Instrument Detection Limit (IDL) (μg L^{-1})	Limit of Detection (LOD) (mg kg^{-1})	Limit of Quantitation (LOQ) (mg kg^{-1})
BADGE	1.0000	0.5	0.010	0.025
BADGE•H_2O	0.9998	1.0	0.010	0.025
BADGE•$2H_2O$	0.9993	5.0	0.010	0.025
BADGE•HCl	0.9991	0.5	0.010	0.025
BADGE•2HCl	0.9993	1.0	0.010	0.025
BADGE•H_2O•HCl	0.9998	0.5	0.010	0.025
BFDGE	0.9998	1.0	0.010	0.025
BFDGE•$2H_2O$	0.9992	10.0	0.010	0.025
BFDGE•2HCl	0.9983	1.0	0.010	0.025
NOGE•3ring	0.9999	0.5	0.010	0.025
NOGE•4ring	0.9997	0.5	0.010	0.025
NOGE•5ring	0.9985	2.5	0.010	0.025
NOGE•6ring	0.9984	2.5	0.010	0.025

Table 4. Extraction recoveries at five level concentrations (0.025, 0.50, 1.00, 9.00 and 18.0 mg kg^{-1}) for thirteen monomers, i.e. BADGE, BFDGE, NOGE and their derivatives.

Analyte	Recovery, % (average ± SD)				
	0.025 mg kg^{-1}	0.50 mg kg^{-1}	1.00 mg kg^{-1}	9.00 mg kg^{-1}	18.0 mg kg^{-1}
BADGE	87.32 ± 9.44	100.14 ± 4.06	102.50 ± 1.98	102.86 ± 5.86	100.46 ± 3.11
BADGE•H_2O	82.90 ± 4.86	95.37 ± 5.08	103.23 ± 2.68	101.96 ± 6.02	98.92 ± 1.06
BADGE•$2H_2O$	80.18 ± 18.60	97.02 ± 3.94	103.63 ± 3.40	98.88 ± 5.77	96.22 ± 3.50
BADGE•HCl	82.00 ± 13.08	99.48 ± 5.89	100.99 ± 1.76	100.07 ± 7.79	102.81 ± 3.19
BADGE•2HCl	93.06 ± 12.25	97.52 ± 7.65	103.02 ± 3.02	100.15 ± 9.10	101.21 ± 9.32
BADGE•H_2O•HCl	78.11 ± 6.23	97.05 ± 4.98	98.83 ± 4.80	97.82 ± 5.91	97.2 ± 5.28
BFDGE	92.93 ± 4.65	99.21 ± 3.51	104.80 ± 1.68	102.96 ± 5.59	103.48 ± 6.10
BFDGE•$2H_2O$	74.29 ± 11.89	97.19 ± 6.71	100.94 ± 4.70	97.45 ± 6.00	97.72 ± 3.65
BFDGE•2HCl	85.84 ± 14.96	95.03 ± 8.79	100.04 ± 3.91	94.19 ± 8.72	93.06 ± 6.69
NOGE•3ring	87.17 ± 7.92	100.46 ± 5.34	100.66 ± 8.64	104.11 ± 5.23	102.93 ± 4.72
NOGE•4ring	81.97 ± 8.44	92.63 ± 9.01	98.38 ± 5.94	101.30 ± 5.62	101.15 ± 4.43
NOGE•5ring	78.33 ± 7.20	91.68 ± 8.01	98.16 ± 5.61	100.85 ± 5.70	100.34 ± 1.96
NOGE•6ring	84.87 ± 13.07	95.72 ± 7.05	95.75 ± 6.28	102.79 ± 5.48	103.05 ± 6.64

Robustness was also investigated following EUR 24105 EN (Table 5) [33]. These results showed non-significant differences using a two-tailed t-test at a 95% confidence level. Thus, the developed method was suitable to determine thirteen compounds of BADGE, BFDGE, NOGE and their derivatives.

Table 5. Experiment sets of robustness by varying seven parameters, i.e. NaCl, $MgSO_4$, ACN, weight, C18, PSA and $MgSO_4$ for cleanup step.

Parameters		Experimental sets							
Developed method (+)	Varied condition (-)	1	2	3	4	5	6	7	8
A) NaCl 1 g	a) NaCl 3 g	+	+	+	+	-	-	-	-
B) $MgSO_4$ 4 g	b) $MgSO_4$ 6 g	+	+	-	-	+	+	-	-
C) ACN 10 mL	c) ACN 15 mL	+	-	+	-	+	-	+	-
D) weight 10 g	d) weight 5 g	+	+	-	-	-	-	+	+
E) C18 25 mg mL^{-1}	e) C18 50 mg mL^{-1}	+	-	+	-	-	+	-	+
F) PSA 0 mg mL^{-1}	f) PSA 25 mg mL^{-1}	+	-	-	+	+	-	-	+
G) $MgSO_4$ 150 mg mL^{-1}	g) $MgSO_4$ 300 mg mL^{-1}	+	-	-	+	-	+	+	-

3.5 Sample analysis

The developed method was applied to the canned foods purchased from local markets in Thailand. The several food matrices were performed, for example, tuna in oil, tuna in brine, tuna in mineral water, mackerel in tomato sauce, sardine in tomato sauce and tuna in mayonnaise etc. The concentrations were found as shown in Table 6 and revealed the suitability of this developed method in the analysts of canned food and complying to regulatory limit [6]. The quality control was also performed by using triplicate, recovery and precision that fell in acceptable range. In comparison with other methods [20], the LOD and LOQ of this study were a little higher than the performance in vegetable products due to fat and oil in fish canned food. However, there were various ranges of LOD and LOQ either fish and vegetable canned food [3, 13-17,19, 23], Sun et al. gave the similar limit of this research [15]. The BADGE was found in below detectable concentration, which may cause from its transformation in food matrix during long period of storage.

Table 6. Average concentrations (mg kg^{-1}) of BADGE, BFDGE, NOGE and their derivatives in canned foods.

Sample No.	Average concentrations (mg kg^{-1})												
	BADGE	BADGE·H$_2$O	BADGE·2H$_2$O	BADGE·HCl	BADGE·2HCl	BADGE·H$_2$O·HCl	BFDGE	BFDGE·2H$_2$O	BFDGE·2HCl	NOGE 3 ring	NOGE 4 ring	NOGE 5 ring	NOGE 6 ring
1	n.d.	n.d.	0.86	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
2	n.d.	n.d.	0.32	n.d.	0.03	0.03	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
3	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
4	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
5	n.d.	n.d.	0.72	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
6	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
7	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
8	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
9	n.d.	n.d.	n.d.	n.d.	0.63	0.05	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
10	n.d.	n.d.	n.d.	n.d.	0.07	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
11	n.d.	n.d.	0.20	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
12	n.d.	n.d.	n.d.	n.d.	n.d.	0.03	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.
13	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.	n.d.

n.d.: *not detected. The sample details were 1) Mackerel in tomato sauce: brand A, 2) Sardines in tomato sauce, 3) Sandwich tuna in brine, 4) Salmon spread, 5) Sardines in tomato sauce, 6) Mackerel in tomato sauce: brand C, 7) Tuna green curry, 8) Tuna nam prik pad, 9) Tuna in soybean oil (Tuna sandwich), 10) Tuna in spring water (Tuna sandwich), 11) Mackerel in tomato sauce: brand D, 12) Tuna in brine tuna steak and 13) Tuna in mayonnaise.*

4. Conclusion

The reliable method was investigated to simultaneously determine BADGE, BFDGE, NOGE and their derivatives in canned fish. The matrix solid dispersion or QuEChERS method and LC-MS/MS was successfully applied with high efficiency which was validated and obtained good accuracy and precision with the pure standard calibration. The MEF was also applied and gained more accurate and compensate any error during measurement step. This method also provided the benefits of low LOD and LOQ in 0.010 mg kg^{-1} and 0.025 mg kg^{-1}, confirmation using specific ratio of precursors and product ions, less time, labor and expense, as well as complying with Commission Regulation (EC) No. 1895/2005.

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