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Trace determination of bisphenol A and phytoestrogens in infant formula powders by gas chromatography–mass spectrometry

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Abstract

This investigation describes a reliable and sensitive method for simultaneously determining bisphenol A (BPA) and two major phytoestrogens, daidzein and genistein, in powdered milks and infant formulas by gas chromatography–mass spectrometric analysis after trimethylsilylation. To reduce the matrix interference associated with the constituents of the formulas, the dissolved formula solutions were firstly ultra-centrifuged and the analytes in the supernatant were then extracted using a C_{18} solid-phase extraction column. The accuracy and precision of the method were determined and the technique was successfully employed to measure trace concentrations of BPA, daidzein and genistein in powdered formulas. The results show that BPA, daidzein and genistein were detected in all the testing samples ($n = 6$) at concentrations from 45 to 113 ng/g (except one infant formula), 20 to 2050 ng/g and 21 to 6510 ng/g, respectively. The highest concentrations of daidzein and genistein (i.e., 2050 and 6510 ng/g) were detected in a soy-based powdered infant formula. The quantitation limits were 1.0 ng/g for BPA, and 10 ng/g for daidzein and genistein using 0.5 g powdered milk samples.

Keywords: Infant formulas; Food analysis; Bisphenol A; Phytoestrogens; Phenols; Endocrine disrupters

1. Introduction

Society is increasingly concerned with natural and synthetic chemicals that exhibit estrogenic affects. Correspondingly, screening programs have been established to identify chemicals that act as endocrine disrupters. Plant-derived phytoestrogens are a group of such chemicals, and are present in many human foodstuffs. The consumption of phytoestrogens has been associated with a variety of protective affects [1–4]. However, their biological characteristics differ from those of natural estradiol or other endogenous estrogens in humans. For instance, their possible affects on some enzymes, inhibiting steroid metabolization, anti-proliferative and anti-angiogenic processes, and other biological effects have been described [5–8]. High concentrations of phytoestrogens, especially daidzein and genistein, have been detected in soy-based infant formulas [9–11]. The daily exposure of infants to these phytoestrogens may produce thymic and immune abnormalities [9–11]. Even exposure to these phytoestrogens early in life may offer long-term health benefits for those with hormone-dependent diseases; but during the critical periods of infant development, the very young children may exhibit qualitatively and quantitatively distinct sensitivities to the estrogenic functions induced from these endocrine-related compounds. However, the concentrations of these phytoestrogens in infant formula are unclear, and very few manufacturers state on the labels, that their products contain phytoestrogens. Hence, customers cannot evaluate the possible health affects of phytoestrogens in infant formulas. Moreover, powdered milk (including infant formulas) may have hormonally active contaminants introduced in the manufacturing process or leached from containers. Bisphenol A (BPA) is a major one, it is a monomer used to produce polycarbonate, epoxy resins and polyester-styrene resins [12–17]. These resins are widely used in the canned food and beverage packing, leading to potential human exposure [12,13]. BPA residue has been detected in wine, mineral water and food stored in plastic containers [14–16], and in food from cans coated with epoxy resin lacquers [12,17]. BPA has recently been found to be one of the more potent anthropogenic estrogen mimics [18–20]. It can induce progesterone receptors in cultured human breast cancer cells (MCF-7) at a rate 5000-fold weaker than 17β-estradiol (E_2), and can also bind to estrogen receptors, with affinities 2000-fold weaker than that of E_2. BPA contamination of various canned foodstuffs

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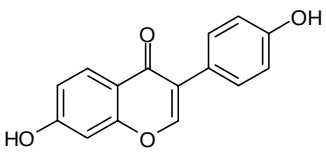
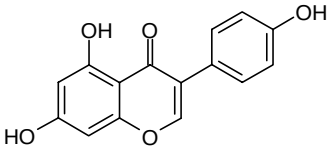
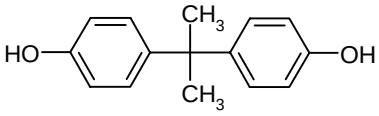


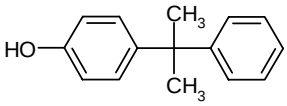
Daidzein (De)



Genistein (Ge)



Bisphenol A (BPA)



Cumyphenol (CP)
as a surrogate

Fig. 1. Structures of daidzein, genistein, BPA and cumyphenol.

has been investigated [12–17]. However, none of these reports have discussed the contamination of canned powdered milks by BPA. Structures of BPA, daidzein and genistein are shown in Fig. 1.

Numerous analytical methods for BPA and phytoestrogens have been developed. HPLC with UV absorbance is a widely used method for the analysis of these compounds [10,21–24]. However, most of the time mass spectrometric technique is needed to confirm positively the presence of these compounds after HPLC–UV detection. LC–MS with electrospray represents a powerful method for determining BPA and phytoestrogens [25–27], but the required equipment and maintenance are expensive, and not readily available. GC or GC–MS is not only more readily available in many analytical laboratories, but also provides a higher chromatographic resolution with a capillary column and greater sensitivity. GC–MS has been used routinely to determine BPA and phytoestrogens after derivatization to enhance volatility [28–39]. However, information on the investigation of the derivatization of these compounds with sterical hindrance in the multiple hydroxyl groups is rare. Since BPA and phytoestrogens are present at ng/g (ppb) levels in regular powdered milks, the primary derivatization requirement is to form a single derivative with a mass spectrum that contains ions of high diagnostic value is preferred to obtain maximum sensitivity and specificity.

As part of a larger effort to characterize the impact of BPA and phytoestrogens in dietary components consumed by infants and young children, we have developed a reliable, selective and sensitive method to routinely and simultaneously determine trace levels of bisphenol A, daidzein and genistein in powdered milks and infant formulas, by GC–MS analysis after trimethylsilylation. Powdered milks are ultra-centrifuged and the analytes are extracted using a C_{18} solid-phase extraction (SPE) column. This work represents a preliminary study of endocrine-related compounds in powdered milks and infant formulas sold in Taiwan, to support children's health and food safety programs.

2. Experimental

2.1. Chemicals and reagents

Unless noted otherwise all high-purity chemicals and solvents were purchased from Aldrich (Milwaukee, WI, USA), Tedia (Fairfield, OH, USA) and Merck (Darmstadt, Germany), and were used without further purification. Reagent-grade bisphenol A was purchased from TCI (Tokyo Chemical Industry, Tokyo, Japan). The daidzein, genistein, cumyphenol (as a surrogate), *N*,*O*-Bis(trimethylsilyl)trifluoroacetamide (BSTFA), and trimethylchlorosilane (TMCS) were purchased from Aldrich-Sigam (Milwaukee, WI, USA). [$^2H_{12}$] Chrysene chrysene-d_{12}; (as an internal standard) was purchased from ChemServices (West Chester, PA, USA). 1,4-Dithioerythritol (DTE) was purchased from Fluka (Riedel-de Haën, Hannover, Germany). Stock solutions of each analyte (1000 μg/ml) were prepared in methanol. Mixtures of the analytes for working standard preparation and sample fortification were also prepared in methanol. All stock solutions and mixtures were stored at −10 °C in the dark.

2.2. Derivatization procedures

Adequate volume of each working standard solution was added to Reacti-Vial (Pierce & Warriner, Chester, UK) and

evaporated to dryness under nitrogen at 60 °C. The residue was derivatized by adding 100 μl of the silylating agent, containing BSTFA + TMCS + DTE (1000:10:2, v/v/w). The vial was vortex mixed and heated at 80 °C (between 60 to 90 °C; 80 °C being chosen, see Section 3) for 30 min (among 15, 30, and 60 min; 30 min being chosen, see Section 3). After cooling, the derivatized solution was evaporated to dryness, and the residue was redissolved in 100 μl of chloroform containing 10 μg/ml of chrysene-d_{12} as an internal standard by vortex. The trimethylsilyl (TMS) derivatives of analytes were then made ready for GC–MS analysis.

2.3. Sample preparation

The powdered infant formulas and follow-up formulas were purchased from local supermarkets or nationwide wholesale markets. Accurately weighted portion of 0.5 g of powdered sample was dissolved in 10 ml 50% (v/v) ethanolic solution, and 5 μg/ml cumyphenol was added as a surrogate. The sample solution was mixed for 10 min with a magnetic stir bar, and ultra-sonicated for 2 h around 4 °C. The solution was then ultra-centrifuged for 60 min at 16 000 rpm, the supernatant was filtered through 0.45 μm membrane filter (Gelman Scientific, Ann Arbor, MI, USA) [40], and then applied to a C_{18} SPE cartridge (Supelclean ENVI-18 SPE, Supelco, Bellefonte, PA, USA). Before extraction, each SPE cartridge was conditioned with 3 ml of methanol and 3 ml of deionized water on an SPE manifold (VacMaster, IT Sorbent Technology, Cambridge, UK). Supernatant was passed through the SPE cartridge at a flow rate of about 2–3 ml/min via a siphon tube with the aid of a vacuum. When the extraction was completed, the cartridge was dried under vacuum for 2 min. The analytes were then eluted from the cartridge with 3 ml methanol. The extract was dried by $MgSO_4$ and then completely evaporated to dryness by a stream of nitrogen, and made ready for TMS derivatization (as described in Section 2.2).

The recovery experiments were performed using the spiked powdered milk samples. Known amounts of BPA and phytoestrogens, dissolved in 100 μl of methanol were evenly distributed on top of the powdered milk by a glass syringe. The sample was then mixed by tumbling for 30 min. The spiked samples were stored in a tightly closed brown glass bottle at room temperature for 24 h, and made ready for sample extraction procedures as described above.

2.4. GC–MS analysis

Analyses were performed on a HP-5890 Series II gas chromatograph directly coupled to a HP-5973 mass-selective detector (Hewlett-Packard, Wilmington, DE, USA) operating in the electron impact (EI) and selected ion monitoring (SIM) modes. Samples (1 μl) were injected with the injection temperature at 300 °C in the splitless mode. A DB-5MS capillary column (30 m × 0.25 mm I.D., 0.25 μm film, J&W, Folsom, CA, USA) was used. The GC temperature program was as follows: 100 °C for 2 min, followed by a temperature ramp at 10 °C/min to 250 °C, then temperature ramp at 5 °C/min to 300 °C, and hold for 5 min. The transfer line was set at 280 °C. Full scan EI data was acquired under the following conditions: mass range 50–550 *m/z*, scan time 1 s, solvent delay 13.5 min. Quantitation of the analytes was carried out in the SIM mode, once their characteristic masses were selected from their full spectra. The selected masses were *m/z* 372 and 357 for BPA, *m/z* 398 and 383 for daidzein, *m/z* 414 and 399 for genistein, as well as *m/z* 284 and 269 for cumyphenol, at dwell time of 100 ms/ion/scan. In all cases, they correspond to the ions of M^+ (molecular ion) and $[M\text{-}CH_3]^+$, respectively. The detector was tuned with perfluorotributylamine (PFTBA) by using the autotune program. The electron energy was 70 eV, and the electron multiplier was operating at 200 to 300 V above the autotune value with the high energy dynode on.

3. Results and discussion

3.1. Method optimization

Trimethylsilylation is a commonly used derivatization procedure for analyzing bisphenol A and phytoestrogens using GC–MS [28,33,34,38,39]. Analytes with multiple hydroxyl groups can generate multiple derivatives, reducing the sensitivity and selectivity of the determination. Hence, the formation of a single derivative with a mass spectrum that contains ions of high diagnostic value is preferred to maximize sensitivity and specificity. Reaction with BSTFA alone yielded more than one derivative with various fractions of mono- and bis-*O*-TMS derivatives for these multiple hydroxyl-substituted compounds. Similar results were observed in our previous study when BSTFA as the lone derivatizing agent for estrogenic chemicals with multiple hydroxyl groups [i.e., 17β-estradiol (E_2), 2-hydroxyestradiol (2-OH-E_2), estriol (E_3), etc.] [41]. The addition of a stimulator in BSTFA was recommended to increase the derivative

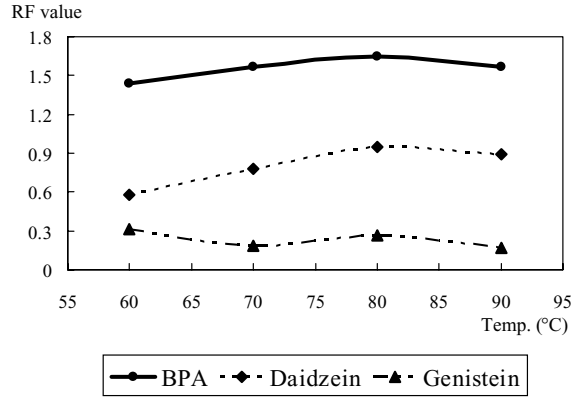


Fig. 2. The effect on the response factors of TMS derivatives of the reaction temperature at 30 min.

efficiency for multiple hydroxyl analytes [41–43]. TMCS is one of the commonly used stimulators in TMS derivatives [42,43]. According to our previous experience, the use of BSTFA with 1% TMCS as a derivatization solution was sufficient to form one main multiple TMS-substituted derivatives, and also to improve the chromatograms and generate the highest average peak areas and quantitative results [41]. No significant increase in the sylilation efficiency was observed when more than 5% TMCS was added, except for genistein. Less than 10% of tris-O-TMS derivatives of genistein was detected, may be due to the sterical hindrance of the keto group at position 4. Here, a small amount of DTE was also added to stabilize the derivatization solution and enhance the peak abundance, as suggested by Smets et al. [44]. Thus, using BSTFA with 1% TMCS plus 0.2% DTE as derivatization solution was sufficient to form one main bis-*O*-TMS-substituted derivatives for these three analytes.

The influence of reaction temperature and time were investigated. Fig. 2 shows that the response factors did not significantly differ among the TMS derivatives obtained over

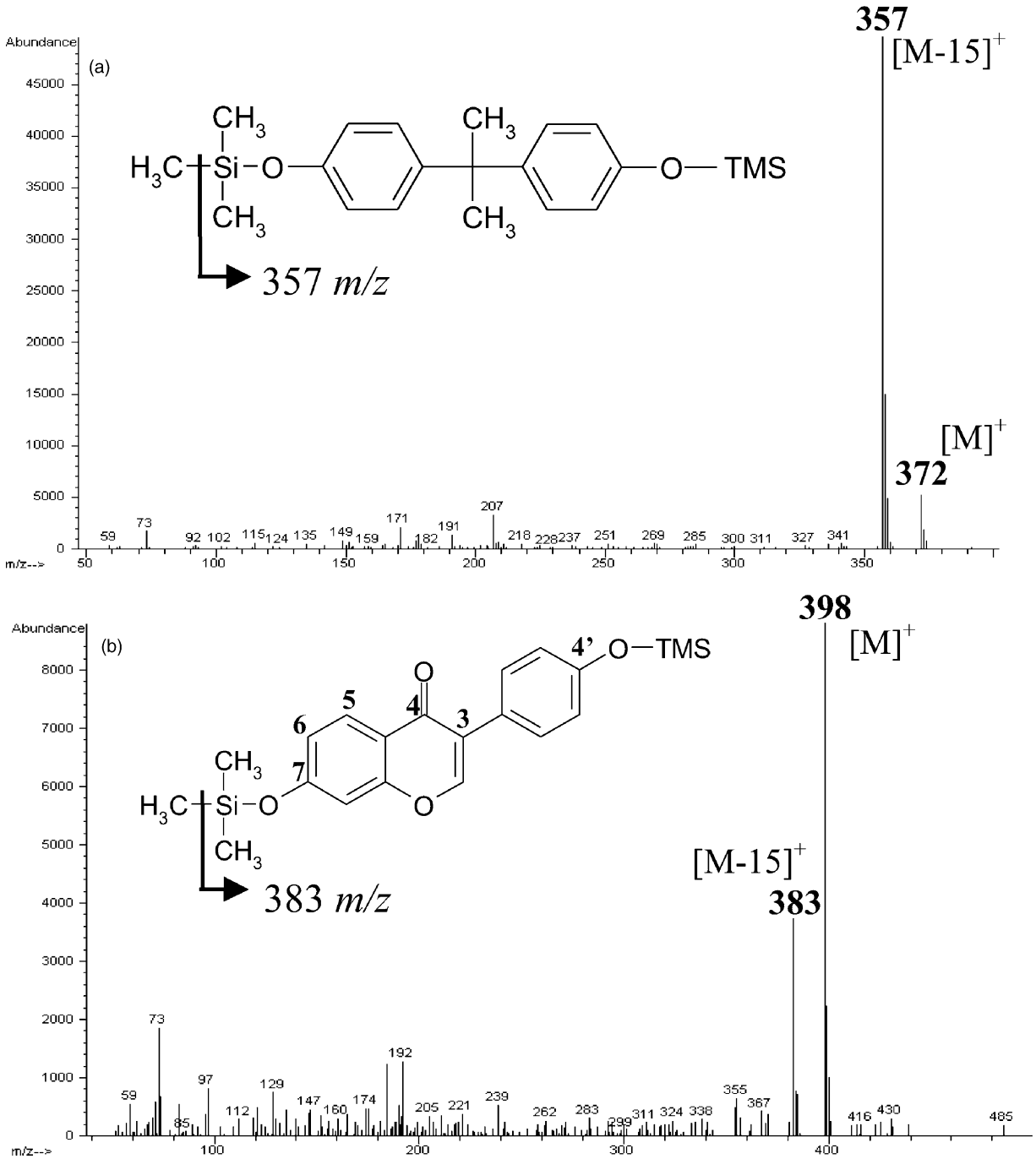


Fig. 3. The profiles of full-scan EI mass spectra and tentative fragmentation of the bis(trimethylsilyl)ether derivatives of the analytes: (a) BPA, (b) daidzein and (c) genistein.

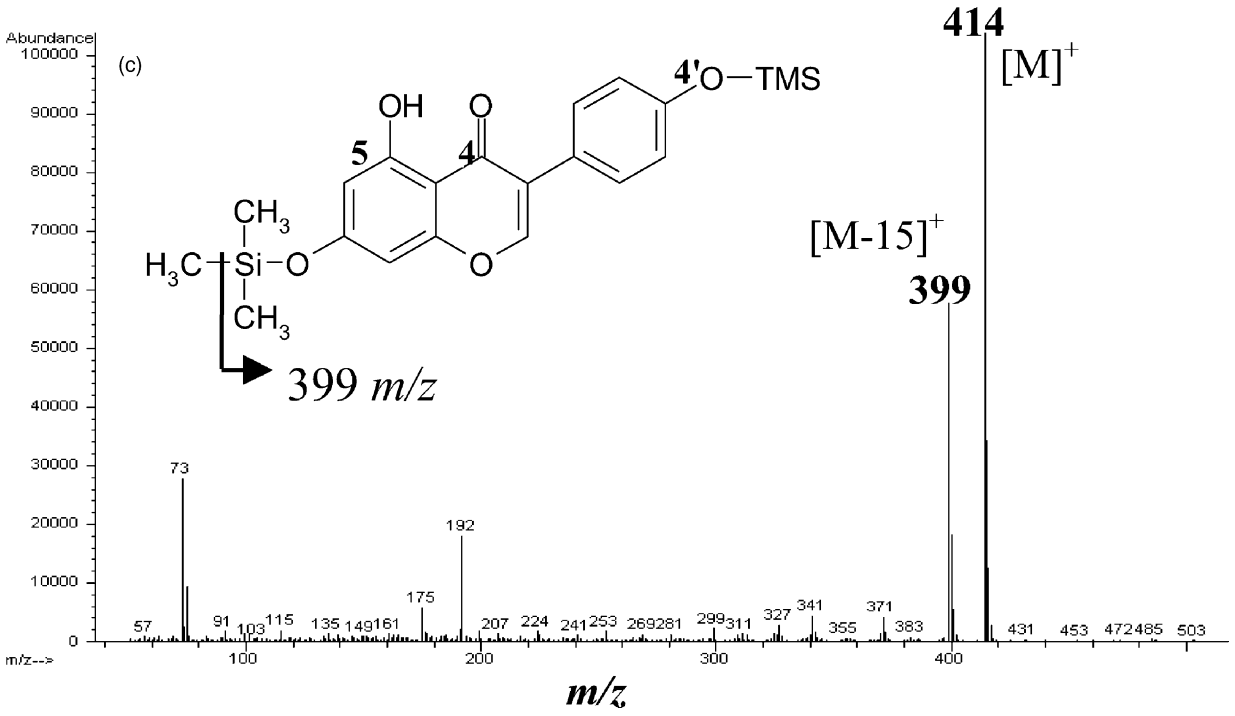


Fig. 3. (*Continued*).

the four reaction temperatures (60, 70, 80 and 90 °C) at 30 min, except for that of daidzein. According to the results, the temperature required for this step is not critical, provided that 80 °C is high enough to complete the TMS derivatization. The affect of reaction time was also evaluated. The response factors were similar at 15, 30, and 60 min (data not shown) at 80 °C. Therefore, the final derivatization conditions chosen were: 100 μl BSTFA with 1% TMCS plus 0.2% DTE solution added to the dried residue and heated at 80 °C for 30 min.

3.2. Mass spectra of derivatives

Fig. 3 displays the EI mass spectra and tentative fragmentation of the bis-*O*-TMS derivatives. These derivatives show a common fragmentation pathway. Either the molecular ions $[M]^+$ or the $[M\text{-}CH_3]^+$ ions were the base peaks in all the derivatives, therefore, to be used as the quantitation ions to obtain maximum detection sensitivity and specificity in the SIM mode. The EI spectrum pattern of genistein provided direct evidence that the hydroxyl group at position 5 was not derivatized possibly due to the steric hindrance of the keto group at position 4. All derivatives displayed an ion at *m/z* 73 $[(CH_3)_3Si]^+$ which was characteristic of the TMS group and commonly observed in all TMS derivatives.

3.3. Method validation and applications

Following the results obtained in the derivatization study, BSTFA with 1% TMCS plus 0.2% DTE is recommended for screening purposes because of the formation of more

Table 1
Analytical reproducibility

Sample	Analytes			Cumyphenol (surrogate, %)
	BPA	Daidzein	Genistein	
Deionized water				
Spike recovery (%) ($n = 3$)	92[a] (7)[b]	96 (2)	94 (4)	90 (2)
Infant formula (lactose-free)				
Background conc. (ng/g)	n.d.	86	140	120
Spiked recovery (%) ($n = 5$)	79[a] (9)[b]	81 (7)	83 (6)	105 (9)

n.d. Not detected at method quantitation limit 1.0 ng/g for BPA.
[a] The spiked recovery.
[b] The relative standard deviations (RSD, %) of spiked recovery are given in parentheses.

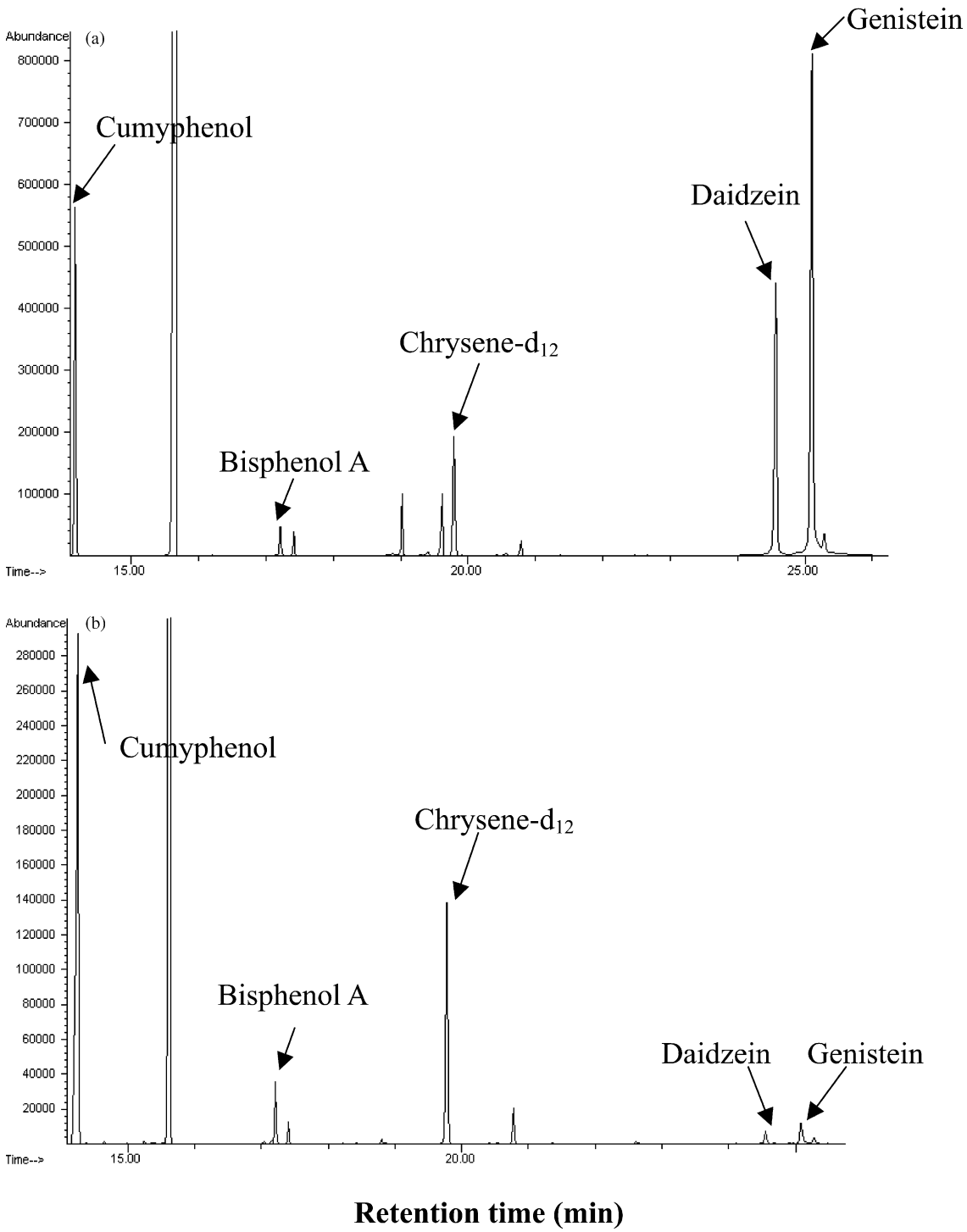


Fig. 4. The typical chromatograms of analytes obtained in SIM mode of the samples from (a) a soy-based infant formula, and (b) a follow-up formula-I.

stable derivatives and one primary derivative for each analyte. The quantitation limits of these compounds by using TMS derivatives were 1.0 ng/g for BPA, and 10 ng/g for daidzein and genistein in 0.5 g powdered milk samples, defined at a signal-to-noise ratio (S/N) $\geq$10. The quantitation of the analytes was calculated from the five-level calibration curve, as indicated by the response factors, covering the range 0.01 μg/ml to 0.5 μg/ml for bisphenol A, and 0.1 μg/ml to 15 μg/ml for daidzein and genistein, each divided by the fixed concentration of a internal standard [45–47]. The precision of the calibration curve, as indicated by the relative standard deviation (RSD) of response factors, was 5, 11, 13 and 4% for BPA, daidzein, genistein and cumyphenol, respectively. The correlation

Table 2
The contents of BPA and phytoestrogens found in powdered milks

Sample	Analytes (ng/g)			Cumyphenol (surrogate, %)
	BPA	Daidzein	Genistein	
Infant formula (Soy-based, $n = 3$)	45[a] (4)[b]	2050 (10)	6510 (8)	89 (5)
Follow-up formula-I	44	37	137	97
Follow-up formula-II	113	20	21	71
Follow-up formula-III	57	26	27	94
Follow-up formula-IV (Hypoallergenic formula, $n = 3$)	57[a] (27)[b]	69 (20)	99 (11)	18 (24)

[a] Average concentration of analytes detected in the samples ($n = 3$).
[b] The RSD (%) of the analyte concentrations are given in parentheses.

coefficients exceeded 0.998 for all four compounds. The curve covered a range equivalent to the concentration of the analytes in final extract.

The recovery of the method was firstly evaluated using deionized water samples spiked with known amounts of analytes (i.e., 10 ng for BPA; 100 ng for daidzein and genistein) and cumyphenol (100 ng; as a surrogate). The precision of the method, as indicated by the RSD of the recovery, was assessed using three independent pretreatment and extractions of analytes from deionized water samples. The recoveries were above 90% and RSD ranging from 2 to 7%, as shown in Table 1. Five replicate 0.5 g powdered milk samples were each spiked to obtain the final concentrations of 4 ng/g for BPA, and 400 ng/g for daidzein and genistein. Average recovery ranged from 79 to 105% with RSD ranging from 6 to 9%, indicating good recovery and repeatability of the method (Table 1). Five powdered infant and follow-up formulas were employed as test samples after appropriate pretreatment, as described in Section 2.3. Fig. 4 shows the typical chromatograms of analytes, obtained in the SIM mode, of the samples from (a) a soy-based infant formula, and (b) a follow-up formula-I. The peaks were identified and quantitated using retention times with characteristic ions and response factors, respectively. Table 2 shows that BPA, daidzein and genistein were detected in all the testing samples at concentrations from 45 to 113 ng/g, 20 to 2050 ng/g and 21 to 6510 ng/g, respectively. The highest concentrations of daidzein and genistein were detected in a soy-based infant formula. Recovery of the surrogate in the samples of powdered formulas ranged from 71% to 97%, except for the follow-up formula-IV. Triplicate analyses of soy-based infant formula and follow-up formula-IV were also performed to evaluate the analytical precision. The RSD of the concentrations of the analytes in soy-based infant formula ranged from 4 to 10%. However, the high variation and low surrogate recovery of the follow-up formula-IV may be related to the analyte-matrix interaction and the influence of the hydrolyzed enzymes on SPE in this special hypoallergenic formula, as discussed elsewhere [48]. The results indicate that the method is appropriate for analyzing BPA, daidzein and genistein in regular powdered milks and infant formulas.

4. Conclusion

The combination of ultra-centrifugation, SPF and GC–MS (SIM) analysis after trimethylsilylation permits the reliable and rapid determination of trace BPA and phytoestrogens in regular powdered milks and infant formulas. The content of these compounds in special hypoallergenic formulas, which contain hydrolyzed proteins, may not be analyzed by this method. Preliminary results indicate that BPA, daidzein and genistein are ubiquitous in regular powdered infant and follow-up formulas. The varying concentrations of BPA reveal that BPA finds its way into food via miscellaneous pathways and at different stages of powdered milk production. Traces of phytoestrogens have also been detected in infant and follow-up formulas other than soy-based infant formula. Consequently, the content of these compounds must be routinely monitored in the production of infant and follow-up formulas, and reported to meet consumer health and food safety concerns.

Acknowledgements

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