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ORIGINAL PAPER

Kinetic migration studies of bisphenol-A-related compounds from can coatings into food simulant and oily foods

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Abstract The migration rule of bisphenol-A-related compounds from can coatings into canned food and oil-based simulant was explored, and the quantification and confirmation of these compounds were performed with an ultra-performance liquid chromatography coupled to tandem mass spectrometry (UPLC-MS/MS). The correlation between the molecular weight, migration time, the initial concentration and the migration level of contaminants was investigated. A quantitative structure–property relationship (QSPR) model of migration was established corresponding to the migration of these migrants in the oily simulant at 55 °C, which served as an accelerated shelf life testing (ASLT) with the use of elevated temperature to simulate long-term storage at room temperature. The correlation coefficient (R), leave-one-out cross-validation coefficient (R_{LOO}) and external validation coefficient (Q_{ext}) for the established model were all above 0.9000. What is more, application of the developed model was tentatively validated with three oily canned foods, whose results showed that the model can play an important role in providing a reference for the estimation of migration behavior of bisphenol-A-related compounds in canned food.

Keywords Bisphenol-A-related compounds · Can coatings · Food simulant · Migration mathematical models · QSPR model

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Introduction

Migration of potentially toxic compounds in epoxy resins used for packaging materials, especially in lining commercial cans, is a very important food safety issue, because of their potential endocrine disruptors. Bisphenol-A (BPA) has been known to have estrogenic activity since 1936 [1], and chronic low-level exposure to this compound has posed serious concerns about effects on human development and reproductive health [2–6]. In order to avoid risk to human, the Commission Regulation 1895/2005 [7] has established the specific migration limit (SML) for these bisphenol-A-related compounds in material and articles intended to come into contact with food or food simulants.

Migration of bisphenol-A diglycidyl ether (BADGE) and its derivatives is normally determined by using food simulants. According to EU Directive 82/711EEC [8], water for aqueous foods, 3 % acetic acid in water for acidic aqueous foods, 10 % aqueous ethanol for alcoholic products and edible oil for fatty foods, the four simulants were used for testing migration from food contact materials (FCMs). People tend to apply actual test (direct analysis with real foods and food simulants without model prediction), semitest and semiempirical model (an effective tool which is established based on the migration rule of real packaged food and is used to predict migration of certain contaminant) to analyze migration of compounds in packaging materials. In the actual test, Luo et al. [9] and Chen et al. [10] have investigated the effect of food contents, storage time and storage temperature on the migration of BADGE and its derivatives through real canned samples and simulation test. Lopez-Cervantes et al. [11] have investigated the migration of BPA from food-grade PVC (polyvinyl chloride) films into foodstuffs using food simulants and found that migration from a given film was

greatest into olive oil. However, analyzing the migration of compounds from packaging materials into food is very complicated by using different analytical methods, such as liquid chromatography with fluorescence detection (HPLC-FLD) [12–14], gas chromatography combined with mass spectrometry (GC–MS) [15] and HPLC–MS/MS (tandem mass spectrometry) [16–20]. Likewise, the kinetics experiment is time-consuming and laborious. Compared to experimental methods, model prediction is more convenient and economical and, most importantly, it can predict the migration behavior of contaminants in packaging materials.

Several studies have revealed that migration of contaminants from packaging material to liquid substance is a theoretically predictable physical process [21]. Maria de Fatima et al. [22] have investigated the modeling migration from paper into a food simulant, and a kinetic model based on Weibull distribution function was established to describe migration from plastic additives. Silva et al. [23] have used Fick's second law [24] to investigate the kinetic migration studies from packaging films into meat products. Some others like Wang et al. [25] have used QSPR model to investigate the migration of ester additives in food-grade PE (poly ethylene) films. And these established models can provide a precise and efficient prediction of migration level of contaminants in food-packaging materials. Furthermore, this saves experimental testing, time and economic resources for the food industry. To the best of our knowledge, no studies have been reported about the migration mathematical models concerning the migration behavior of bisphenol-A-related compounds from can coatings into foodstuffs. This paper is the first that established a kinetic QSPR model [26] of bisphenol-A-related compounds from can coatings into food simulant using an accelerated experiment and tried to validate the model with commercial canned foods. Migration levels of some detected and representative compounds in canned foods were evaluated and compared to those observed migration values in order to validate the applicability of the established model.

Materials and methods

Reagents and materials

Standards of bisphenol-A (BPA, CAS no. 80-05-7), bisphenol-A diglycidyl ether (BADGE, CAS no. 001675-54-3), bisphenol-A (2, 3-dihydroxypropyl) glycidyl ether (BADGE·H_2O, CAS no. 076002-91-0), bisphenol-A bis (2, 3-dihydroxypropyl) ether (BADGE·$2H_2O$, CAS no. 005581-32-8), bisphenol-A (3-chloro-2-hydroxypropyl) glycidyl ether (BADGE·HCL, CAS no. 013836-48-1), bisphenol-A bis (3-chloro-2-hydroxypropyl) ether (BADGE·2HCL, CAS no. 004809-35-2), bisphenol-A (3-chloro-2-hydroxypropyl) (2,3-dihydroxypropyl) ether (BADGE·H_2O·HCL, CAS no. 227947-06-0), bisphenol F diglycidyl ether (BFDGE, CAS no. 2095-03-6), bisphenol F bis (3-chloro-2-hydroxy-propyl) ether (BFDGE·2HCL, CAS no. No), bisphenol F bis (2, 3-dihydroxypropyl) ether (BFDGE·$2H_2O$, CAS no. 72406-26-9, consists of three isomers p, p-, o, p- and o, o-BFDGE), Novolac glycidyl ether 3-ring (3R-NOGE, CAS no. 158163-01-0), Novolac glycidyl ether 4-ring (4R-NOGE), Novolac glycidyl ether 5-ring (5R-NOGE) and Novolac glycidyl ether 6-ring (6R-NOGE) were purchased from Fluka (Buchts, Switzerland). Figure 1 shows the structures of several standards.

Stock solutions (1 mg mL^{-1}) of each of compounds were prepared by dissolving in acetonitrile (ACN) in dark bottles and used for further dilutions. These solutions were stored at 4 °C for 6 months.

Acetonitrile (ACN) of HPLC grade was obtained from Merck (Darmstadt, Germany), and formic acid of HPLC grade was provided by Tedia (purity 96 %, Fairfield,

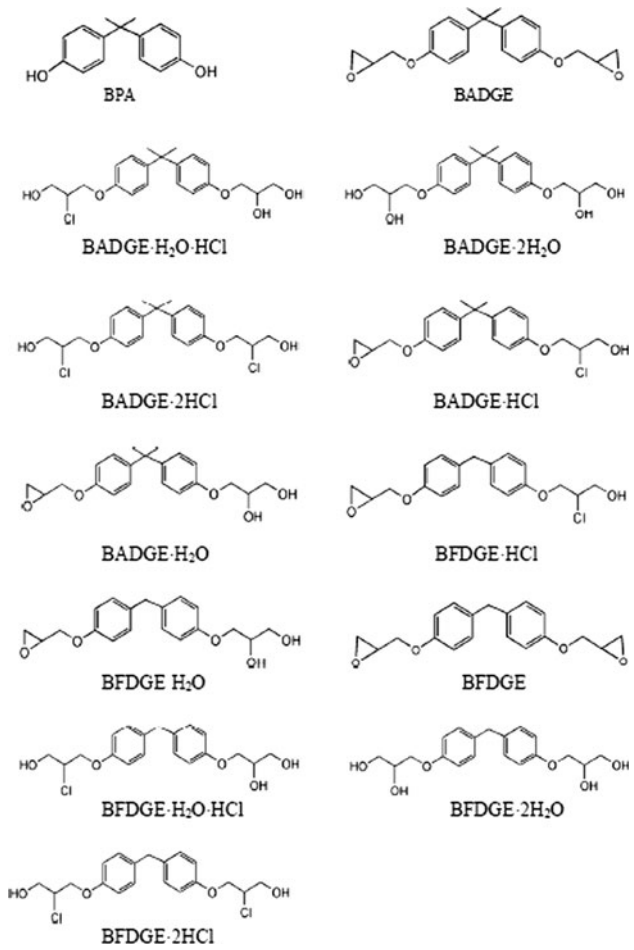

Fig. 1 Structures of several bisphenol-A-related compounds. Only the p, p′- structures of BFDGE and its hydrolysis and chlorinated derivatives are listed

USA). Ultrapure water was obtained from a Milli-Q purification system (Millipore, MA, USA). ACN, acetone, methanol (MeOH) and n-hexane of analytical grade were purchased from QZJH (Zhejiang, China).

Instruments and their conditions

The chromatographic separation was performed on a Waters ACQUITY UPLCTM system. The analyte separation was accomplished on an ACQUITY UPLCTM BEH C18 Column, 2.1 × 100 mm, 1.7 um (Waters Corporation, MA, USA).

MS/MS was API-4000 triple quadrupole linear ion trap (4000 Q TRAP, Applied Biosystems, USA) equipped with a TurboIonSpray^{TM} source. Instrument control, data acquisition and the processing were performed using the associate Analyst 1.5.1 software.

The UPLC-MS/MS condition was set as follows: Analytes were detected by multiple reaction monitoring (MRM) using electrospray ionization (ESI) with both positive and negative modes; column temperature was 30 °C, and the injection volume was 5 uL. Mobile phase was 0.2 % formic acid solution (solvent A) and ACN (solvent B), and the flow rate was 0.4 mL min^{-1}. Gradient elution mode was as follows: 0–1 min, 35 % B; 1–1.5 min, 35–45 % B; 1.5–5 min, 45–75 % B; 5–6.5 min, 75–99 % B; 6.5–8.5 min, 99 % B; and 9–10 min, 65 % B [16, 20].

Samples

In the accelerated experiment, soybean oil was selected as simulant (because of its universal use in oily canned food in China) to mimic oily foods, which was sealed in an empty can during experimental process. Canned fish (precooked *Cirrhinus molitorella*), canned pork paste with mushroom and canned stewed pork were obtained from different companies as soon as the can sealing was finished.

Extraction of bisphenol-A-related compounds from food simulant

Ten milliliters of solution (which was obtained after soaking of can coating with oily simulant—the extraction of the coating was carried out on the coated can—that is the lining of the can) was placed in a tube, followed by addition of 5 mL ACN and then vibrated for 2 min in a vortex mixer. The ACN layer was transferred to a 25-mL spin evaporate bottle and repeated the above steps two times. Finally, the combined ACN layer was evaporated to dry at reduced pressure at 40 °C in a rotary vacuum evaporator. Then the residue was re-dissolved in 1 mL ACN/H_2O (50:50, v/v) and filtered using 0.22-um syringe-driven nylon filters prior to UPLC-MS/MS analysis.

The recovery experiment of extraction procedure was performed with blank oily simulant spiked with three different concentrations (10, 25 and 250 ng mL^{-1}) of standard mixtures. Each spiked concentration was analyzed in triplicate as described above.

Extraction of bisphenol-A-related compounds from packaging materials and canned foods

Extraction from can coatings

The cans were washed with warm water and detergents before extraction. Then the clean and dried cans were laid on their sides, half-filled with ACN, sealed with aluminum foil paper and then stored at room temperature for 24 h. During the storage period, the cans were put in 100 °C water bath soaking for 1 h. Then the ACN extract was transferred into a flask and evaporated to appropriate volume at reduced pressure at 40 °C in a rotary vacuum evaporator. Then appropriate amount of water was added to the residues in order to have the final 1:1 ACN/H_2O. Finally, about 1 mL extract was filtered through a 0.22-um nylon filter prior to UPLC-MS/MS analysis. In order to demonstrate the extraction was completed, the extraction procedure was repeated again and then the extract was analyzed by the same UPLC-MS/MS method.

Extraction from food content

First, approximately 5.0000 g samples was homogenized and then placed in Teflon-lined vessels, followed by addition of 10 mL n-hexane and 5 mL acetone. Second, after tightly sealing with the caps, the Teflon-lined vessels were placed into a Microwave extractor (Mars, CEM, Matthews, NC, USA), heated for 10 min to 105 °C and kept for 5 min and then cooled down to 30 °C to transfer the content into centrifuge tubes. Third, the extract was centrifuged at 12,000 rpm for 10 min, and then the supernatant was further extracted twice with 5 mL ACN. Fourth, the combined ACN extract was evaporated to dry at reduced pressure at 40 °C in a rotary vacuum evaporator. The dried residue was re-dissolved in 1 mL ACN/H_2O (50:50, v/v) and filtered using 0.22-um syringe-driven nylon filters. Finally, 10 uL extract was injected into the UPLC-MS/MS system [12, 13, 16].

The recovery experiment of extraction procedure was performed with fortified blank matrixes (spiked with three different concentrations of standard mixtures), which was conducted on canned fish with oil (oil-based canned food).

Migration rule of bisphenol-A-related compounds in canned food and food simulant

In the accelerated migration experiment, the principle of selecting contact time and contact temperature between food and packaging material was based on this rule: In actual using process, the predictable longest contact time and highest contact temperature were chosen when packaging materials were in contact with foodstuffs. Three oil-based canned foods which had been sealed from factory were stored at room temperature for 18 months. During this period, the change of SML concerning several detected bisphenol-A-related compounds was investigated, whose purpose was to provide references for a further understanding of the migration rule of these compounds in canned foods.

Experimental design

Fifteen time points were selected to determine the migration level of three kinds of bisphenol-A-related compounds (BPA, BADGE·HCL·H_2O and BADGE·$2H_2O$) in food simulant, and the principle of selecting time points was as follows: days 1, 2, 3, 5, 7, 9, 12, 15, 18, 22, 26, 30, 35, 40 and 45 were selected as storage time points after can sealing. Consequently, 45 experimental data of migration were obtained for subsequent use.

Three kinds of oily food (canned fish, canned pork paste with mushroom and canned stewed pork) were sent to our library after can sealing in 3 days and then stored in room temperature in order to sustain their shelf life. Then the concentration of bisphenol-A-related compounds in canned food was determined once a month, and figures of their migration trends and levels were obtained. The initial concentration of the migrant in the packaging material is the source of migration, and it has an important effect on the subsequent migration level. So the initial concentration of bisphenol-A-related compounds in can coatings was determined (the procedure of determination of the initial concentration of bisphenol-A-related compounds in packaging material is described in section "Extraction from can coatings"), and its value was set as C_o. The extraction procedure and analysis of bisphenol-A-related compounds in can coatings and food content were performed as described in section "Extraction of bisphenol-A-related compounds from packaging materials and canned foods."

Mathematical models

Based on the investigation of migration rule of bisphenol-A-related compounds in simulant and real canned foods, a migration model of several detected compounds (analytes with high migration levels and detection rates) was established. Correlation analysis between the migration level and the factors which effected migration behavior was conducted. The selected factors included the molecular weights of contaminants (M), migration time (t) and the initial concentration of migrants (C_o). Those variables were selected according to their important effects on the migration of analytes (the importance of their effects on migration process was confirmed by our following migration experimental results and references concerning migration of contaminants [24, 25]). In the accelerated study of canned foods, the use of elevated temperature was often chosen to simulate long-term storage at room temperature [27] and mimic a worst-case situation with regard to the migration level of target compounds. It is generally thought that most commercial canned meat was stored at 55 °C for 30 days that is equivalent to those stored at room temperature for 10 months or longer time [28, 29]. So in our study, the migration level of bisphenol-A-related compounds in canned foods at room temperature can be predicted using the migration model established at 55 °C. Besides, it is not necessary to predict the migration level of contaminants leaching into canned foods in long storage time under 55 °C or higher temperatures, because in the actual using process, no one would store canned food under that high temperature for such a long time. Though some studies pointed out that diffusion coefficient (D_p), which is largely dependent on the change of temperature, is an important parameter that determines the migration process, we did not consider it as a variable. In the experimental design of migration into food simulant, temperature was set as a constant (55 °C), so factors related to temperature became insignificant. A linear regression equation through multiple linear regression (MLR) method coupled with QSPR model [30] in food simulant was established. Soybean oil was chosen as the model simulant (edible oil simulant) to mimic the long-term storage of canned meat. Finally, the established model was validated by internal and external methods [26] to ensure good predictability and applicability. Furthermore, the migration model was tentatively applied to predict the migration trends and estimate the migration levels of several bisphenol-A-related compounds in three oily canned foods. The predicted values and observed values of the migration of contaminants were compared to estimate the actual application power of the developed migration model.

Results and discussion

Optimization of extraction of oily simulant

Extraction solvents (MeOH and ACN) and extraction times were investigated to optimize the extraction of bisphenol-

A-related compounds from oily simulant. The spiked recovery showed that the extraction rate was much higher when ACN was used as the extraction solvent, and three times extraction was much better than one or two times. Therefore, three times extraction with ACN was chosen as the best extraction procedure.

Method validation

Validation data of oily food simulant

Blank oily simulant spiked with three different concentrations of standard mixtures were chosen to validate the accuracy of the analytical method. The average recovery of bisphenol-A-related compounds in oily simulant was in the range of 79.3–93.6 % (data shown in Table 1), whose values were a little lower because of the high viscosity and complicated constitutes of oily simulant, which was exactly the truly reflection of oil-based canned foods.

Validation data of real canned foods

The results of recovery of fortified blank oily food (canned fish) were shown in Table 2. The main recoveries obtained from the oily food were in the range of 75–101 % except for 3R-NOGE, 4R-NOGE and 6R-NOGE. The repeatability of the analytical method was determined by calculating intraday precision expressed as RSD % ($n = 6$, analysis of spiked samples at different times at the same day) values obtained from the spiked samples, whose result showed that the values of RSD did not exceed 10 % for all analytes [16].

Table 1 Average recovery ($n = 3$) of BPA-related compounds in oily food simulant

Analytes	Spiked level (ng/mL)		
	10	25	250
BPA	84.67 ± 3.64[a]	89.55 ± 2.56	90.42 ± 3.17
BADGE·2H$_2$O	75.21 ± 5.68	84.87 ± 3.64	85.30 ± 2.50
BADGE·H$_2$O·HCl	78.90 ± 4.29	88.26 ± 3.25	85.57 ± 3.16
BADGE·H$_2$O	85.84 ± 3.66	83.90 ± 4.03	84.71 ± 4.52
BADGE	80.84 ± 4.37	85.71 ± 2.60	84.59 ± 3.24
BFDGE	87.32 ± 4.18	85.49 ± 4.47	89.88 ± 3.26
BADGE·2HCl	79.35 ± 4.34	88.16 ± 3.88	84.46 ± 3.52
BADGE·HCl	88.37 ± 3.37	87.68 ± 2.41	88.20 ± 2.68
BFDGE·2HCl	79.77 ± 5.37	88.46 ± 3.29	86.42 ± 4.26
BFDGE·2H$_2$O	78.12 ± 5.12	79.69 ± 4.66	86.56 ± 4.27
3R-NOGE	79.43 ± 5.53	77.89 ± 5.14	81.84 ± 3.76
4R-NOGE	81.84 ± 3.76	86.36 ± 4.25	85.20 ± 3.07
5R-NOGE	79.58 ± 4.86	84.25 ± 3.29	87.44 ± 3.78
6R-NOGE	77.17 ± 5.13	80.12 ± 4.26	82.26 ± 3.17

[a] Average recovery % ± RSD, $n = 3$

Table 2 Average recovery ($n = 6$) of BPA-related compounds in fortified blank oily food (canned fish with oil) [16]

Analytes	Spiked level (ng/g)		
	10	25	250
BPA	82.52 ± 5.21[a]	83.95 ± 4.56	85.48 ± 4.23
BADGE·2H$_2$O	84.87 ± 5.67	91.86 ± 4.26	101.77 ± 2.97
BADGE·H$_2$O·HCl	75.78 ± 7.66	87.62 ± 6.93	94.58 ± 4.48
BADGE·H$_2$O	79.26 ± 4.92	91.64 ± 4.10	93.07 ± 3.05
BADGE	82.44 ± 6.96	84.01 ± 6.79	87.00 ± 3.15
BFDGE	76.35 ± 4.74	78.96 ± 3.60	83.75 ± 2.85
BADGE·2HCl	75.08 ± 7.79	79.23 ± 6.98	87.97 ± 3.58
BADGE·HCl	74.48 ± 6.44	87.68 ± 2.41	88.20 ± 2.68
BFDGE·2HCl	79.77 ± 5.37	86.46 ± 4.80	85.66 ± 4.65
BFDGE·2H$_2$O	78.39 ± 4.22	84.56 ± 4.05	88.11 ± 2.94
3R-NOGE	68.64 ± 7.42	83.77 ± 5.46	94.03 ± 4.63
4R-NOGE	65.38 ± 6.73	68.39 ± 4.82	79.42 ± 5.17
5R-NOGE	75.9 ± 4.41	85.45 ± 2.76	91.86 ± 3.20
6R-NOGE	72.14 ± 7.33	76.54 ± 5.37	86.58 ± 5.05

[a] Average recovery % ± RSD (intraday precision, $n = 6$)

Migration rule of bisphenol-A-related compounds into food simulant

The empty cans were filled with 90 % volume soybean oil simulant and then placed in a thermostat as soon as can sealing in order to investigate the relationship between migration trend of these bisphenol-A-related compounds into food simulant and storage time.

Figure 2 shows that there are increasing trends of content for BPA, BADGE·H$_2$O·HCL and BADGE·2H$_2$O along with storage time change, especially in the former 30 days. The increase in concentration is due to the normal diffusion process of these contaminants to the medium in contact with the resin. And this migration behavior is of little

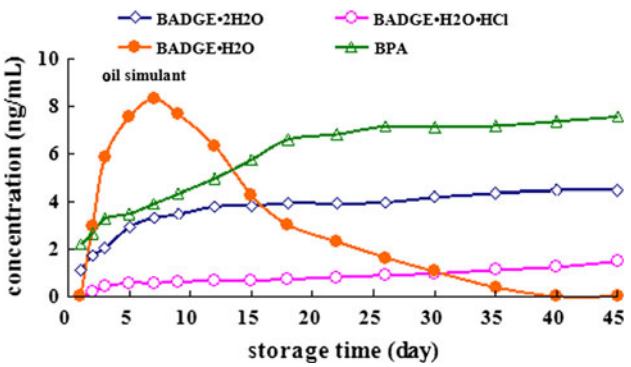

Fig. 2 Migration of bisphenol-A-related compounds into oil simulant at 55 °C

difference with the findings of Munguia-Lopez et al. [31] who found the storage time had little significance on the migration of BPA in their experiment. This is because they mainly investigated the effect of commercial heating process on BPA migration, and in that case, storage time had little effect on the migration compared to heating factor. But in the latter 15 days, the migration level started increasing slowly. It also appeared that the migration level of BADGE·H_2O into oil simulant increased in the former 7 days and then reduced dramatically and even disappeared at last. And this may be explained by the fact that BADGE·H_2O translated into other bisphenol-A-related derivatives in the later storage time or reacted with the food simulant to produce some new compounds that are not being detected [32].

Migration rule of bisphenol-A-related compounds in canned food

The migration trends of several detected bisphenol-A-related compounds in three oily canned foods during 18-month storage are shown in the following figures.

Figure 3 shows that the migration level of detected bisphenol-A-related compounds changed apparently as storage time goes on. The migration trend implies that migration levels in the latter 12 months were significantly different from that in the former 6 months, indicating that these contaminants were very dependent on storage time. This finding is consistent with the result observed by Cabado et al. [33] who investigated the migration of BADGE and BFDGE in canned seafood and found that the migration of the two compounds was very dependent on storage time. The migration level in the latter 15–18 months was about 3–20 times more than that in the former 3 months (the biggest migration level of BADGE·HCL was up to 66.216 ng g^{-1} under 18-month storage in canned fish, while the migration levels of some compounds were even 0 at the first month). For most bisphenol-A-related compounds, the expected observation was confirmed: The longer the contact time, the higher the migration levels. In addition, the migration level of BADGE·HCL·H_2O changed significantly in canned pork paste with mushroom and canned pork, and it kept increasing drastically after 12-month storage (their migration level increased to 31.725 and 45.748 ng g^{-1} after 18-month storage, respectively). The same phenomenon with BADGE·HCL was also observed in Fig. 3a. The migration level of BFDGE, BADGE·$2H_2O$ and BADGE·2HCL increased slightly after 12-month storage and leveled off in later storage. Even in some samples, the migration level of BADGE·$2H_2O$ reduced in later storage time. It could be explained by the formation of reaction products between –OH of BADGE·$2H_2O$ and other food ingredients, such as amino acids and proteins [34], and the amount of denatured ingredients surpassed that of the migration level. Besides, –OH is apt to combine Cl, especially in the presence of sodium chloride under slightly acidic conditions [35]; thus, BADGE·H_2O and BADGE·$2H_2O$ may translate into the chlorinated derivatives like BADGE·HCL and BADGE·H_2O·HCL. Furthermore, the developed products such as BADGE·HCL can also react with amino acids (such as Met) and form the adduct BADGE·HCL·SCH_3 and so on [34].

Establishment of QSPR migration model of bisphenol-A-related compounds in food simulant

The general guidelines for the development of statistically robust and predictive QSPR models are the following steps:

1. Establish reliable experimental data using reliable quantitative measurements of the target compounds.
2. Divide the underlying database into training and test sets using diversity sampling algorithms.
3. Develop training set models using available QSPR methods or commercial software. Characterize these models with internal validation parameters.
4. Validate training set models using external test set and calculate the external validation parameters.
5. Finally, explore and exploit validated QSPR models for possible mechanistic interpretation and prediction [30].

Establishment of migration model

Table 3 shows the molecular weights and initial concentrations of several contaminants. The 45 experimental data in Table 4 which were used to establish a migration model came from our migration experiment as described in "Experimental design" section. A multiple linear regression analysis was conducted concerning the M, t and C_o and the migration level of the analytical compounds (using Origin8.0 software or Excel 2003), and then the following migration equation in soybean oil simulant at 55 °C was established:

$$Y = 13.6041 - 0.0292M + 0.0689t - 0.0062C_o$$
$$N = 45,\ R = 0.9409,\ \mathrm{SD} = 0.80,\ F = 105.37,$$
$$P = 2.6\mathrm{E}-19 < 0.05, \quad (1)$$

where N is the number of regression sample, R is correlation coefficient, SD is the standard deviation, F is Fisher's test value, and R_{LOO} is the correlation coefficient of leave-one-out (LOO) cross-validation test. P value stands for the statistical significance of correlation for the whole equation

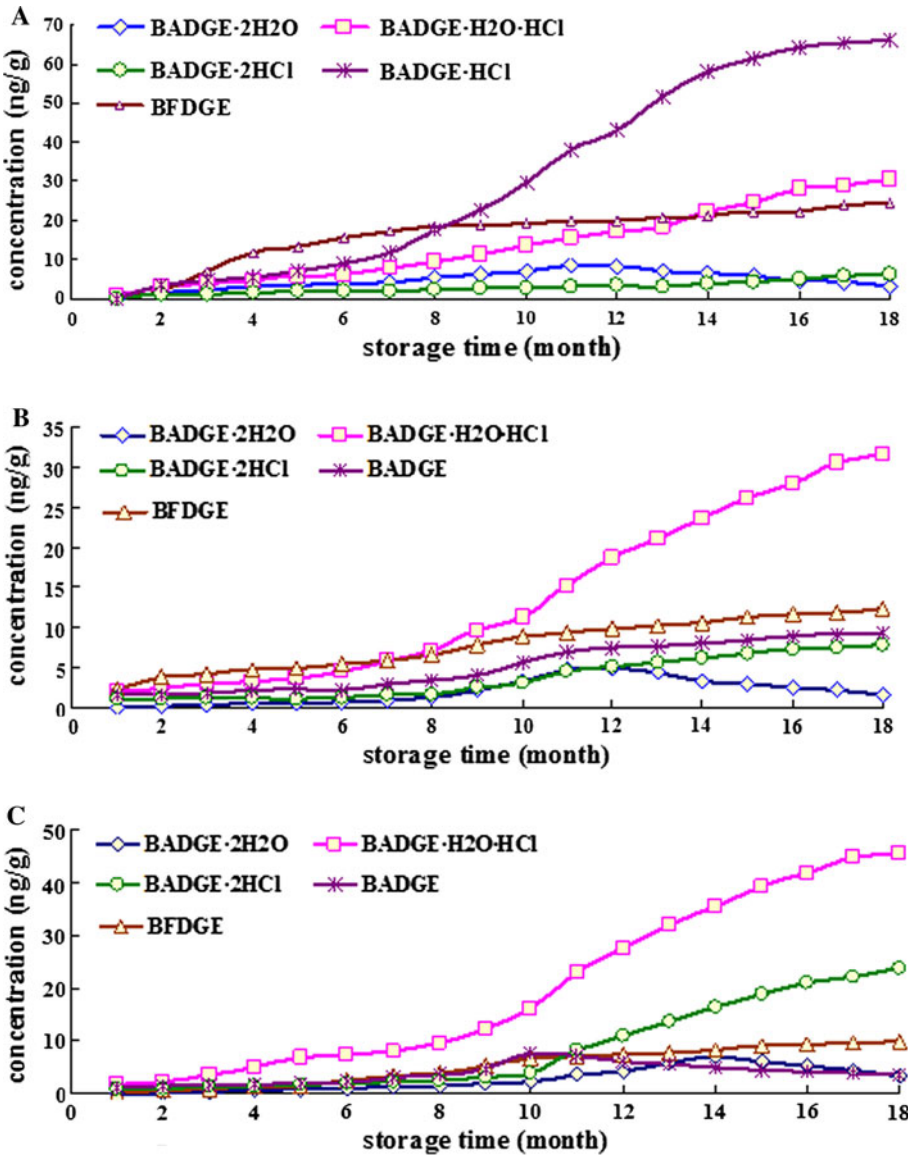

Fig. 3 Migration of bisphenol-A-related compounds from three kinds of oily canned food at room temperature during 18 months. **a** Canned fish, **b** canned pork paste with mushroom, **c** canned pork

Table 3 Molecular weight and initial concentration of several bisphenol-A-related compounds

Analytes	BPA	BADGE·2H_2O	BADGE·H_2O·HCl	BADGE·HCl	BADGE·2HCl
MW (g/mol)	228.12	376.19	394.15	376.14	412.12
C_o (ug/6 dm^2)	455.09	67.73	419.91	86.34	448.33

(confidence coefficient 95 %; $P < 0.05$ is considered as suggestive of a statistical significance); Table 5 shows the statistical significance of each variable in the equation, and the result implies that all the independent variables used for establishing the model are of statistical significance; Table 7 shows the analysis of inter-correlations between the individual values of the independent variables, whose results showed that all the values of $|R| < 0.8$, so there are no significant inter-correlations between the three variables.

Equation (1) implied that the migration level of bisphenol-A-related compounds into oil simulant at 55 °C has an obvious correlation with M, t and C_o. At the same time, it has a negative correlation with molecular weight, just as Wang et al. [25] showed that the molecular weight of ester additives had a negative correlation with their migration into PE film. In addition, the storage time has a positive correlation with the migration level, and this phenomenon complies with the experimental results we conducted. Overall, the developed model can reflect well

Table 4 Migration level of three bisphenol-A-related compounds in oil simulant at 55 °C during 45 days

Storage time (day)	Migration level (ng/mL)		
	BPA	BADGE·2H_2O	BADGE·H_2O·HCl
1	*2.19*[a]	1.11	*0.00*
2	2.66	1.73	0.17
3	3.30	2.04	0.41
5	3.49	*2.93*	0.57
7	3.91	3.32	0.57
9	4.32	3.47	0.62
12	*4.95*	3.80	*0.65*
15	5.74	3.83	0.67
18	6.60	3.94	0.72
22	6.82	*3.92*	0.81
26	7.16	3.97	0.89
30	7.11	4.18	0.96
35	*7.18*	4.34	*1.12*
40	7.37	4.47	1.24
45	7.56	4.47	1.48

[a] All the *italic* values are test sets. A straightforward random selection was used to create training and test sets. Test sets were selected randomly every six data one by one (from *up* to *down*, and *column* by *column*), and the selected eight data in the table are given in *italics*

Table 5 Analysis of the statistical significance of each independent variable in Eq. (1)

Variable	*P* value	<0.05
M	4.15E−19	Yes
t	6.13E−10	Yes
C_o	8.53E−10	Yes

Table 6 Analysis of the statistical significance of each independent variable in Eq. (2)

Variable	*P* value	<0.05
M	4.78E−16	Yes
t	3.17E−08	Yes
C_o	3.44E−08	Yes

Table 7 Analysis of inter-correlations (R value[a]) between the individual values of the independent variables in Eq. (1)

Variable	M	t	C_o
M	1		
t	−2.9E−17	1	
C_o	−0.48564	−4.1E−18	1

[a] R value stands for correlation coefficient; if $|R| < 0.8$, there are no significant inter-correlations between each independent variable

concerning the migration behavior of our target chemicals in oily simulant.

Validation of migration model

It is suggested that only validated QSPR model can offer a meaningful mechanistic interpretation. In order to validate this QSPR model, several approaches should be done, including Y-randomization [36], robust internal validation strategies, such as leave-one-out cross-validations, and external validation. The correlation coefficient R_{LOO} of LOO cross-validation is the most accepted methods used to validate QSPR models. Although a small value of R_{LOO} in the LOO test typically indicates low predictive ability of a model, the opposite is not necessarily true. So, a high R_{LOO} is the necessary condition for a model to have a high predictive power, but it is not a sufficient condition. In order to estimate the true predictive power of a QSPR model, it needs to compare the predicted and observed activities of a large external test set of compounds that were not used in the model development [37, 38]. The predictive power of a QSPR model can be estimated by Q^2_{ext} defined as follows:

$$Q^2_{\mathrm{ext}} = 1 - \frac{\sum_{i=1}^{\mathrm{prediction}} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{\mathrm{prediction}} (y_i - \hat{y}_{\mathrm{tr}})^2}$$

where y_i and $\hat{y}_i$ are the measured and predicted (in the test set) values of the dependent variable and $\overline{y}_{\mathrm{tr}}$ is the averaged value of the dependent variable for the training set.

Based on the above theory, the 45 experimental data were divided into two sections: the training sets and test sets. A straightforward random selection [39, 40] through activity sampling [41, 42] was used to create training and test sets. Test sets were selected randomly every six data one by one, and the selected eight data in Table 4 are given in italics. Subsequently, the migration model was developed by the following 37 experimental data, and the equation was as follows:

Table 8 Analysis of inter-correlations (R value[a]) between the individual values of the independent variables in Eq. (2)

Variable	M	t	C_o
M	1		
t	0.002751	1	
C_o	−0.49248	−0.00651	1

[a] R value stands for correlation coefficient; if $|R| < 0.8$, there are no significant inter-correlations between each independent variable

$$Y = 13.835 - 0.02985M + 0.0664t - 0.00604C_o$$
$$N = 37,\ R = 0.9436,\ \mathrm{SD} = 0.79,\ F = 89.29,$$
$$R_{LOO} = 0.9436,\ P = 6.45\mathrm{E}-16 < 0.05, \quad (2)$$

External validation: $Q_{\mathrm{ext}} = 0.9318$; the results in Table 6 show that all the independent variables used for establishing the model are of statistical significance; Table 8 implies that there are no significant inter-correlations between the three independent variables.

The selected eight test sets were adopted to validate the predictive power of the developed model, and the calculated value of Q_{ext} was 0.9318. So the results suggested that the established model is of high stability and predictability.

Application of established model of migration—the combination of the migration model and real canned foods

The established model was tentatively used to predict the migration level and trend of several kinds of bisphenol-A-related compounds in some representative oily canned foods (canned fish, canned pork paste with mushroom and canned stewed pork). Variables of M (g mol^{-1}), t (from the 10th to the 18th months after these cans' sealing) and C_o [ug (6 dm^2)$^{-1}$] were put into the migration model (Eq. 1), and the predicted migration values of contaminants were obtained and compared to those observed values. Subsequently, the values of Q_{ext} were calculated to evaluate the fitting of data obtained by the model. Figure 4 shows the migration trend and migration level of these bisphenol-A-related compounds in three oily canned foods at room temperature. Migration levels of these compounds were evaluated and compared to those observed ones, whose results showed a good fitting of data. And most of the external validation correlation coefficients of these compounds were >0.9000, which indicated that the established model had a good stability and predictability when it was used for predicting the migration of bisphenol-A-related compounds in real canned foods.

Figure 4a shows the migration model of BADGE·HCL in canned fish which fits very well to the experimental data, and its external validation coefficient Q_{ext} is 0.9319. What makes the model better is that the predicted migration data and the experimental data have same migration trends, and this phenomenon is what we expected. It also showed that the experimental data are a little bigger than the predictive data and this situation can be explained by the fact that some other kinds of bisphenol-A-related compounds (such as BADGE·H_2O and BADGE·2H_2O) translated into BADGE·HCL and BADGE·2HCL with storage time [35]. Figure 4b–e takes on the same migration trends as Fig. 4a. All the results obtained by the model show a fairly good

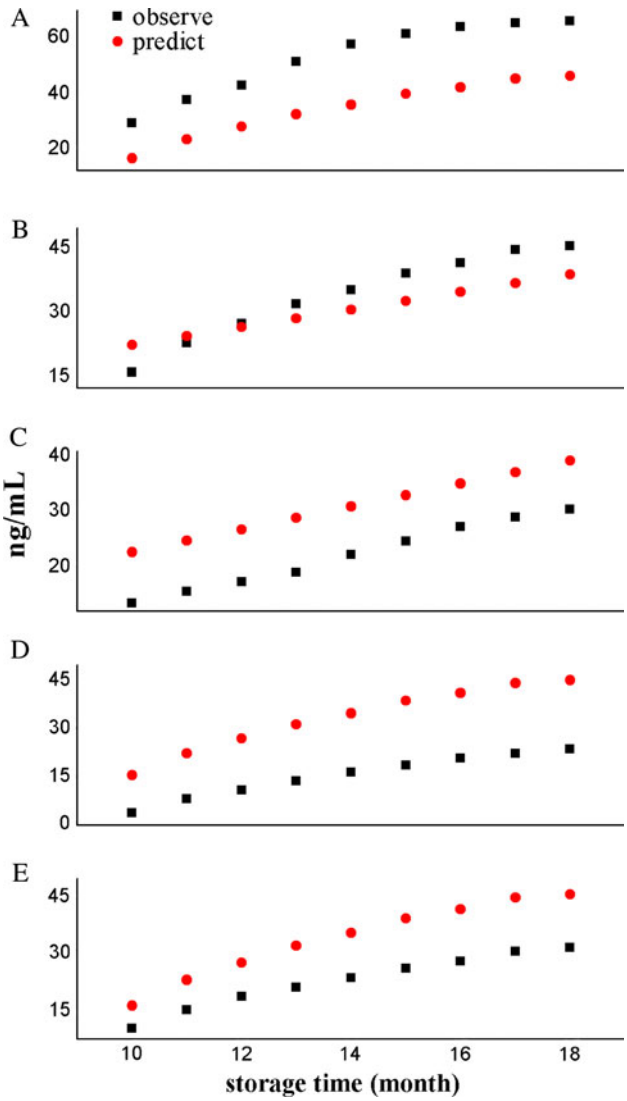

Fig. 4 Migration trend of several kinds of bisphenol-A-related compounds in three oily canned foods at room temperature. **a** BADGE·HCl in canned fish, $Q_{\mathrm{ext}} = 0.9319$. **b** BADGE·$H_2O$·HCl in canned pork, $Q_{\mathrm{ext}} = 0.9802$. **c** BADGE·$H_2O$·HCl in canned fish, $Q_{\mathrm{ext}} = 0.9116$. **d** BADGE·2HCl in canned pork. **e** BADGE·H_2O·HCl in canned pork paste with mushroom

relationship between M, t, C_o and the migration levels. So the developed migration model can provide an important reference to explore the migration of bisphenol-A-related compounds from canned food-packaging materials into foodstuffs.

It also implied that the migration behavior of BADGE·H_2O and BADGE·2H_2O in all the three tested samples did not comply with our developed model (figures not shown). Their migration level started to decrease or even disappeared in the later storage time (shown in Fig. 3). This may be explained by the fact that BADGE·H_2O and BADGE·2H_2O translated into the chlorinated derivatives like BADGE·2HCL and BADGE·H_2O·HCL in the presence

of sodium chloride under slightly acidic conditions or reacted with food ingredients, such as amino acids, protein and sugars [34, 43], which led to the decrease in their migration levels. All those reactions between bisphenol-A-related compounds and food contents can be confirmed by high-resolution mass spectrometric detection, which can explain the unusual behavior of compounds like BADGE·H_2O. Further, more study about migration of these compounds in canned food should be conducted in the future, and consequent modification of the developed migration model in our experiment has to be done.

Conclusion

The developed UPLC-ESI–MS/MS analytical method coupled with the established QSPR model of migration can provide an important reference to explore the migration behavior of bisphenol-A-related compounds in canned foods. Meanwhile, the simple model can simulate and predict the migration of the analytical contaminants, whose results showed that the correlations between migration behavior and M, t and C_o were significant. Furthermore, the model was able to evaluate the worst-case scenario with regard to the amount of compounds capable of leaching into foodstuffs. Taking into account that there are very little data available in the scientific literature regarding food matrices, the most important contribution of the present study is the combination of the established model (developed in oil simulant) and the real canned foods. The migration model can tentatively predict the migration trend of bisphenol-A-related compounds into real canned foods, and in return, canned foods can validate the applicability of the model, whereas the model still needs further data for validation and modification concerning some abnormal migration behavior of some unstable bisphenol-A-related compounds, such as BADGE·H_2O.

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Conflict of interest None.

Compliance with Ethics Requirements This article does not contain any studies with human or animal subjects.

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