

Determination of dimethyl fumarate and other potential allergens in desiccant and antimould sachets

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Abstract A method for the determination of dimethyl fumarate (DMF), benzothiazole (BT) and *tert*-butylphenol (TBP) in desiccant and antimould agents employed for protecting consumer products from humidity and mould has been developed. The method is based on ultrasound-assisted extraction (UAE) followed by GC-MS analysis. Parameters that could affect the extraction of the compounds have been optimised using a multivariate approach. In the final conditions, the extraction is performed using only 0.5 or 1 mL ethyl acetate and applying ultrasound energy for 5 min. Simultaneous extractions could also be carried out in 5 min without losing efficiency. The method was validated showing good linearity ($R^2 > 0.995$). Both intra- and inter-day precisions were studied at several concentration levels, being satisfactory in all cases (RSD <10%). Recovery was evaluated in four real desiccant samples at different compound concentrations, ranging between 87% and 109%. Limits of detection and quantification were in the low nanogramme per gramme level, thus allowing the determination of DMF at concentrations well below the limit established by the recent EU Directive (0.1 µg/g). The proposed procedure was applied to the determination of the target compounds in several desiccant and antimould samples. Although most of them were simply labelled as “silica gel”, more than 70% of the tested samples contained high amounts of DMF, many of them at the high microgram per gramme level. Many samples also showed the presence of the other two potential

allergens. These results demonstrate that the content of the “desiccant” sachets and tablets in consumer products does not usually belong with the label of the desiccant, and hence, the high risk of exposition to the powerful allergen DMF and other potentially harmful chemicals through consumer goods should be a matter of concern.

Keywords Dimethyl fumarate · Benzothiazol · *tert*-Butylphenol · Ultrasound-assisted extraction · GC-MS · Desiccant · Antimould agent · Allergy

Introduction

Consumers have become increasingly familiar with the presence of desiccant sachets in packaged goods such as footwear, leather clothes, handbags, electronics and also in pharmaceuticals and foods. Sachets of desiccants constitute a valuable help for the industry and for consumers since they control the humidity and avoid the damage caused in the materials by moisture and mould, thus preserving the quality, and in this way, extending the self-life of the consumer products. Most desiccant sachets usually contain either clay, minerals or silica gel. However, sachets may also contain substances used to provide or to reinforce the antimould action of the desiccant [1]. In this way, it is worthy of notice that sachets are simply labelled as desiccant, antimould, or even only as “do not eat”.

Two most commonly used desiccants are silica gel and calcium oxide. Silica gel/silica dioxide is a natural mineral which changes to molecular or bead form after purification and processing. Since it is chemically and biologically inert, no harmful health effects will be expected even if it is accidentally ingested in small amounts. Calcium oxide is a white powder which can control humidity effectively by

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Table 1 Main physico-chemical properties of the target compounds

Compound	CAS number	Density (gcm ⁻³)	Molecular weight (gmol ⁻¹)	Boiling point (°C)	Vapour pressure (Pa)	Aqueous Solubility (gL ⁻¹)	Partition coefficient (pKow)
DMF	624-49-7	1.12	144.13	193.0	63.3	22	0.62
BT	95-16-9	1.27	135.19	227.0	1.9	3	2.01
TBP	98-54-4	0.971	150.22	233.7	4.8	9	3.29

keeping the relative humidity below 10%. It is mostly used for packaging dehydrated foods or foods (e.g., biscuits or pastry food) that need to be stored in low-humidity environments. In contact with moisture, calcium oxide becomes caustic and may cause burning sensation, stomach cramps, and diarrhoea if swallowed accidentally. Other desiccants such as activated carbon, clay and calcium chloride, are less commonly used due to their higher cost.

Concern about desiccant sachets started when the first cases of allergic eczemas arose in 2006 related to the use of sofas and chairs manufactured in China. The relationship with the presence of the fungicide dimethyl fumarate (DMF) in desiccant sachets placed under the seats was established by Rantanen [2]. Strong reactions were observed in the most severe case down to 1 mg/kg. Rapidly, new cases of allergy associated to the use of other consumer goods principally footwear, were reported in several European countries, increasing the public concern up to date.

According to clinical tests, the health damage was caused by DMF, which is a powerful fungicide preventing moulds that may deteriorate leather furniture or footwear during storage or transport in a humid climate. DMF, an extreme sensitizer, penetrated through the clothes onto consumers' skin [3] where it caused painful skin contact dermatitis, including itching, irritation, redness, and burns; in some cases, acute respiratory troubles were reported. The presence of DMF is thus a serious risk. From 1998, DMF is banned in biocide formulations for products manufactured in the EU (Directive 98/8/EC); thus, biocidal products containing DMF are not legally available in the community for the treatment of products against moulds, and thus no product manufactured in the EU can legally contain DMF. However, non communitarian producers can use it and thus enter the EU market. The decision adopted by the EU in March 2009 [4] tries to protect EU consumers from the risk

of DMF by banning the importation of contaminated products, and recalling and withdrawing those products already on the market. According to this decision, the presence of DMF in products should be determined against the maximum limit of 0.1 mg per kg of product or part of the product, and the analytical methodology should be able to reliably quantify DMF at this concentration level. This amount is considered to be sufficiently below the concentration of 1 mg/kg, which showed a strong reaction in the patch test mentioned above.

Validated analytical methods for DMF have not been reported in the international scientific literature. HPLC was used for the analysis of DMF and monomethyl fumarate in keratinocytes related to the treatment of psoriasis with fumarates [5]. Rantanen [2] semiquantitatively determined DMF in pieces of chair seats and backrests by a headspace technique and GC-MS, which allowed the first relationship between DMF and severe contact dermatitis cases appeared in Europe.

In addition to DMF, desiccant sachets can contain, adsorb and, hence, spread to the consumer goods other potentially harmful substances. Benzothiazoles are high-production-volume chemicals widely used as biocides in paper and leather manufacturing, as corrosion inhibitors [6, 7], and as vulcanization accelerators in rubber production. Benzothiazole (BT) is known to be present in rubber components, since it is used in vulcanisation processes, and serve as a biocorrosion inhibitor [8]; it can also be a derivative of thiocyanate methylthiobenzothiazole (TMBT), used as a fungicide in leather processing. 4-*tert*-Butyl phenol (TBP) has a wide use as UV light stabiliser, rubber chemical, a corrosion inhibitor, and in insecticides [9], among others. TBP is considered as an endocrine disruptor [10], irritant to the skin, eyes, and respiratory tract. A carcinogenicity study indicated that this chemical has promoted activity of fore stomach carcinogenesis in rats

Table 2 Retention time and ions used for identification and quantification of the target compounds

Compound	Retention time (min)	Quantification ions	Identification ions
DMF	7.23	85,113	85,113,114
BT	10.48	108,135	69,108,135
TBP	11.34	107,135	95,107,135

Table 3 Performance of the GC-MS method

Compound	Linearity		Precision (RSD,%)		LOD (ng/mL)	LOQ (ng/mL)	
	R^2	LOF test					
		F -ratio	P -value	Intra-day ^a ($n=3$)	Inter-day ^b ($n=6$)		
DMF	0.9986	0.52	0.8171	1.3–7.0	1.0–3.1	2.2	7.4
BT	0.9949	2.22	0.1311	3.4–8.0	2.5–5.6	2.4	7.9
TBP	0.9953	0.26	0.9648	0.2–10	0.9–3.5	1.9	6.2

^a Concentration level=0.05–50 µg/mL^b Concentration level=5–50 µg/mL

treated with *N*-methyl-*N'*-nitro-*N*-nitrosoguanidine (MNNG) [11]. Besides, since the structurally related chemical 2(3)-*tert*-butyl-methoxyphenol is a clear carcinogen, the carcinogenic potential of this chemical should not be ruled out.

As a consequence of its widespread use, derivatives of benzothiazoles have been found in the environment, and they should be considered as emerging pollutants. BT has been detected in environmental [12–16] and drinking waters [16], wastewaters [15–18], and sediments [19]. For the determination of this compound, methods combining liquid–liquid extraction (LLE) [12] and solid phase extraction (SPE) [14–17, 19], with GC-MS [12, 14, 19], GC×GC-TOF-MS [15], and LC-MS [16, 17] analysis, have been described.

TBP has been determined in river water after LLE followed by GC-MS and laser-induced fluorescence analysis [20], in seawater and water from an irrigation canal by SPE and HPLC-(ESI)MS [21], in wastewater by continuous LLE-GC-MS [22], and SPE-HPLC-(ESI)MS [23]; in waste landfill leachates by stir bar sorptive extraction-GC-MS after derivatization [9]. TBP has also been detected in outdoor and indoor air [24, 25] and in household dust samples [25].

In this work, a method based on ultrasound-assisted extraction is developed for the determination of DMF, BT and TBP, in desiccant and antimould sachets. To our knowledge, this is the first study about the presence of these harmful compounds in the usual desiccant sachets that can be found in hundreds of consumer goods and are

plentiful in our homes. The method was validated in terms of linearity, precision, sensitivity and selectivity demonstrating its reliability. Obtained LOQ for DMF was widely below the established value in the recently published commission decision [4]. Several desiccant samples obtained from footwear, footwear boxes, clothes, furniture, and accessories were analysed. Almost all the samples presented high concentrations of the target analytes, and more than 70% of the samples presented DMF at high concentration levels, far exceeding the legal limit.

Experimental

Reagents and materials

(*E*)-2-Butenedioic acid, dimethyl ester (dimethyl fumarate, DMF) 97% purity, and benzothiazole (BT) 96 % purity, were purchased from Aldrich (Sigma-Aldrich Chemie GmbH, Steinheim, Germany). 4-*tert*-Butylphenol (TBP) was purchased from Fluka (Fluka Chemie GmbH, Steinheim, Germany). Table 1 shows the physico-chemical properties of the target compounds.

Methanol and ethyl acetate of analytical grade were provided by Merck (Darmstadt, Germany). Stock solutions of each compound were prepared containing concentrations ranged between 2,000–4,000 µg/mL in methanol. Further mixture dilutions were prepared in methanol (for spiking experiments) and ethyl acetate (for external calibration). All solutions were stored in amber glass vials at –20 °C.

Table 4 Factors and levels considered in the experimental design

Factor	Code	Low level (–)	High level (+)	Continuous
Solvent	A	Methanol	Ethyl acetate	No
Volume (mL)	B	1.0	2.0	Yes
Temperature (°C)	C	25	50	Yes
Time (min)	D	5	10	Yes

Real samples of desiccant and antimould sachets and tablets were collected inside of different kinds of clothes, accessories, and footwear, as well as furniture, acquired in several shops and markets of Spain. The content of each sachet was placed in a mortar in order to grind and homogenise the sample. The obtained powder was placed in an amber glass vial and sealed until the extraction and analysis is carried out.

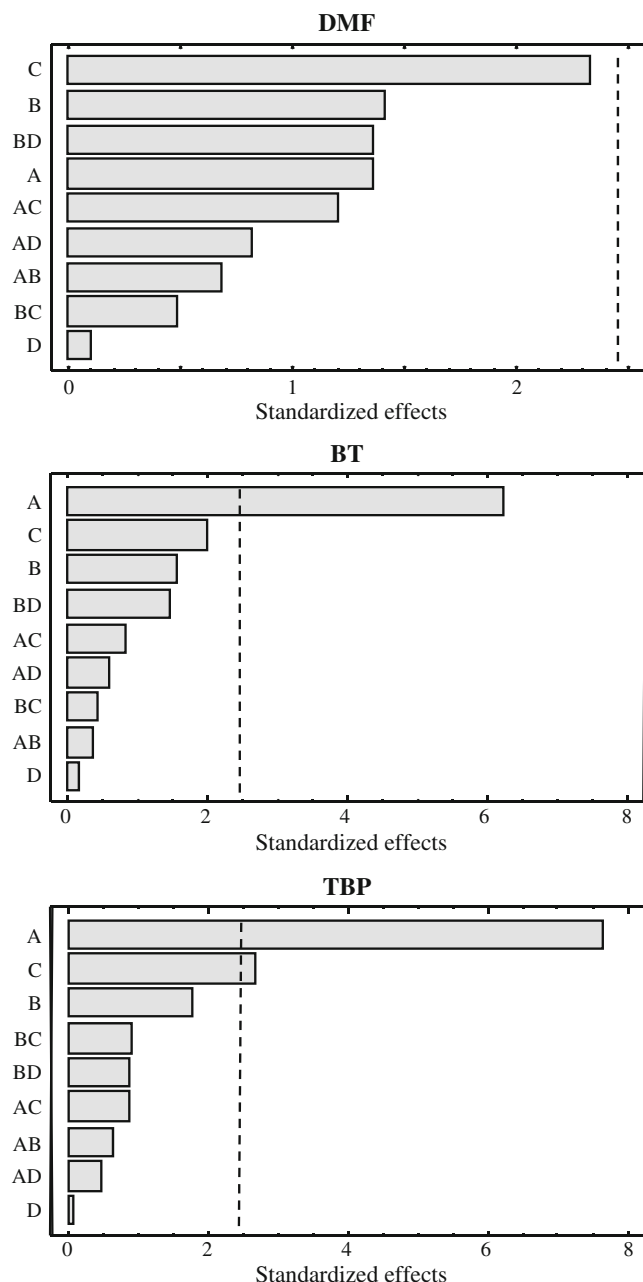


Fig. 1 Pareto charts for the target allergens (see factor keys and levels in Table 4)

Gas chromatography–mass spectrometry

The GC-MS analysis was performed using a Varian 450-GC gas chromatograph (Varian Chromatography Systems, Walnut Creek, CA, USA) coupled to an ion-trap mass spectrometer Varian 240-MS (Varian Chromatography Systems) with a waveboard for multiple MS (MS^n) analysis; and equipped with an automatic injector CP-8400. The system was operated by Varian MS workstation v6.9.1 software.

Separation was carried out on a HP5 capillary column (30 m×0.32 mm i.d., 0.25 μ m film thickness) from Agilent Technologies (Palo Alto, CA, USA). Helium (purity 99.999%) was employed as carrier gas at a

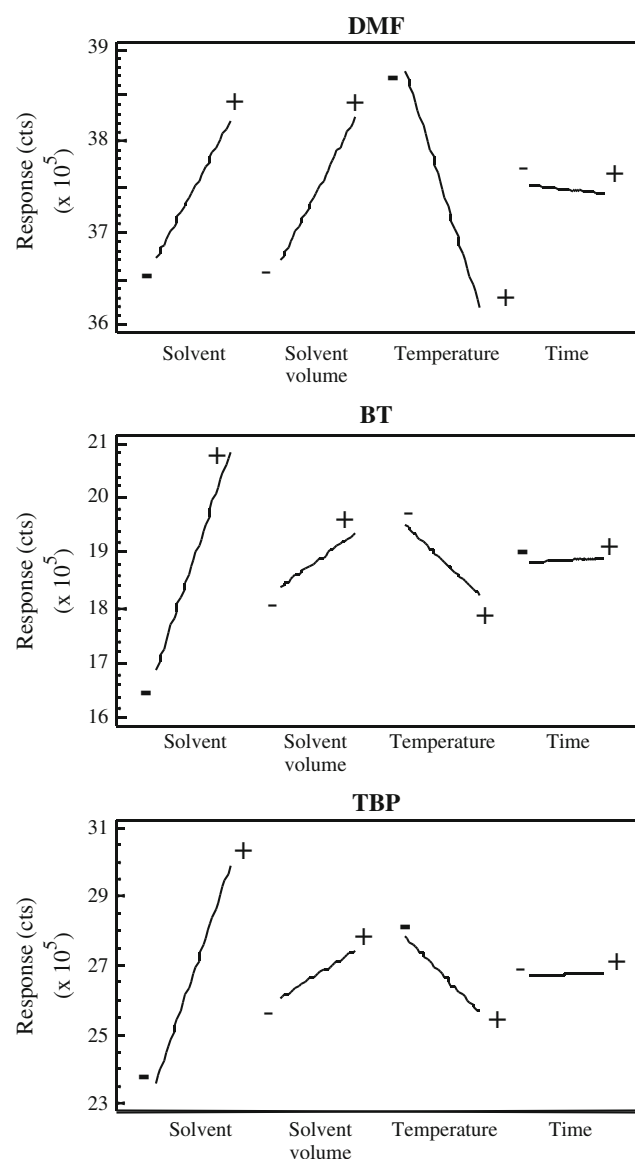


Fig. 2 Main effects plots for the target allergens (see factor keys and levels in Table 4)

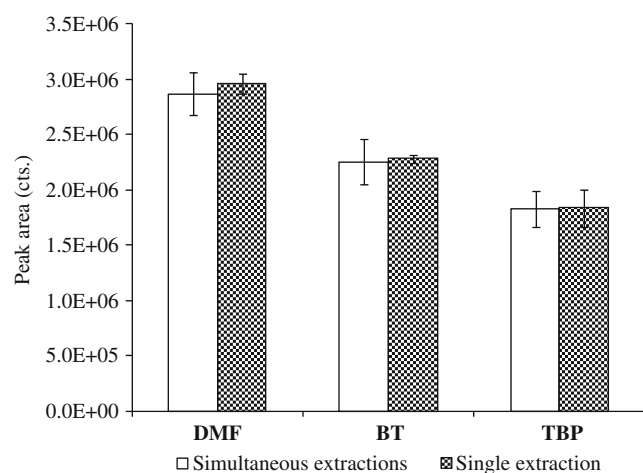


Fig. 3 Comparison of responses between single and simultaneous extractions ($n=6$)

constant column flow of 1.5 mL min^{-1} . The GC oven temperature was programmed from 45°C (held 2 min) to 150°C at $10^\circ\text{C min}^{-1}$ (total analysis time = 12.5 min). Splitless mode (held 2 min) was used for injection, the split flow was set at 20 mL min^{-1} and the injector temperature was kept at 260°C .

The ion-trap mass spectrometer was operated in the electron impact ionisation mode ($+70 \text{ eV}$) using an external ionisation configuration. Manifold, ion trap, ion source and transfer line temperatures, were maintained at 40, 150, 200 and 280°C , respectively. In the full-scan mode the mass range was varied from 50 to 300 m/z at three microscans average, starting at 4 min and ending at 12.5 min. The filament emission current was $25 \mu\text{A}$. The analytes were positively identified by comparison of their mass spectra and retention times to those of standards. The identification and quantification ions and retention times for each target compound are listed in Table 2.

Ultrasound-assisted extraction

The selected volume (0.5, 1 or 2 mL, depending on the experiment) of the organic solvent (ethyl acetate or methanol) was added to the glass vial containing 50–500 mg of sample powder, and sealed with a headspace aluminium cap furnished with PTFE-faced septum. The analytes were extracted from the samples to the organic solvent using an ultrasound bath (Ultrasons Med-II, J.P. Selecta, Barcelona, Spain) at 40 kHz of ultrasound frequency and 200 W power at $25 \pm 3^\circ\text{C}$ or $50 \pm 3^\circ\text{C}$ for 5 or 10 min depending on the experiment. Afterwards, the extract was filtered through a $0.22 \mu\text{m}$ Millex®-GV filter (13 mm diameter; Millipore, Bedford, USA). When it was convenient, extracts were diluted previously to the injection in the chromatographic system.

In the final optimised conditions, samples (50–500 mg) were sonicated with ethyl acetate (0.5–2 mL) for 5 min at $25 \pm 3^\circ\text{C}$. Blanks were periodically run during the analysis to confirm the absence of contamination.

Results and discussion

First experiments were conducted to optimise the chromatographic separation of the target analytes as well as to select the quantification ions to obtain maximum signal-to-noise ratio. The chromatographic conditions are summarised in the experimental section, and the identification and quantification ions are presented in Table 2. The GC-MS method was validated in terms of precision, linearity, and detection and quantification limits.

To evaluate method linearity, a calibration study was performed using standards prepared in ethyl acetate. The calibration range was from 10 ng/mL to 50 $\mu\text{g/mL}$, with seven calibration levels and two to three replicates by level. The method exhibited a direct proportional relationship between the amount of each analyte and

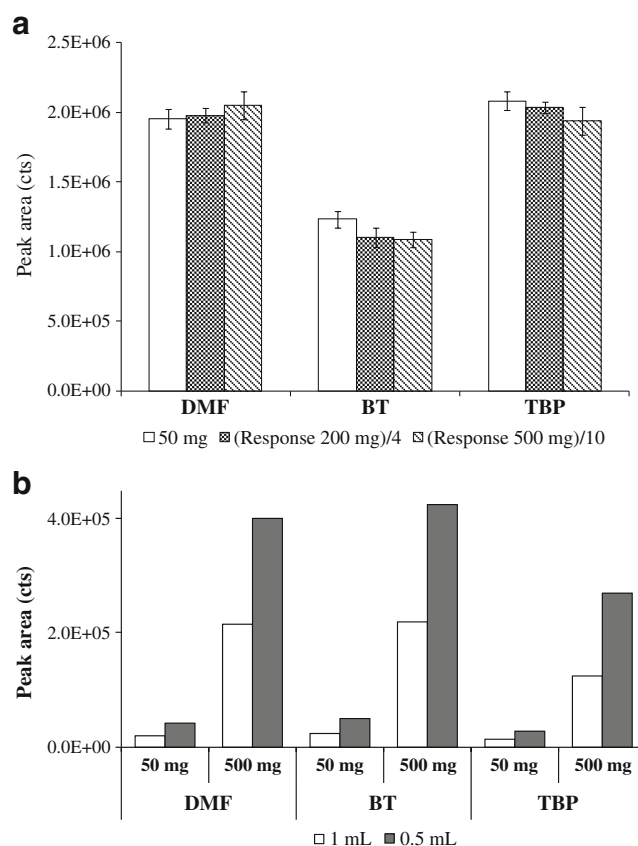


Fig. 4 A) Comparison of responses using different amounts of sample. B) Comparison of responses using different solvent volumes

Table 5 Performance of the proposed UAE-GC-MS method

Compound	Intra-day RSD (%; n=5)				Inter-day RSD (%; n=5)	Recovery (%)				LOD (ng/g)	LOQ (ng/g)
	Addition level (µg/g)					Addition level (µg/g)					
	1	10	100	500		100	1	10	100		
DMF	5.3	2.2	3.8	4.1	3.7(8.0 ^a)	89	103	109	108	5.0	17
BT	2.1	4.6	3.8	5.2	5.1	103	95	92	89	11	36
TBP	9.9	6.7	3.1	3.7	3.8	98	94	87	99	12	39

^a Addition level=500 µg/g

the chromatographic response with a determination coefficient (R^2)>0.9986 (Table 3). To validate the regression data, an analysis of variance was performed. The lack-of-fit (LOF) test is designed to determine whether the selected model is adequate to describe the experimental data. The test compares the variability of the proposed model residuals to the variability between observations at replicate values of the independent variable. Results of the LOF test for the calibration range considered, at a confidence level of 95%, are also shown in Table 3. Since p values are greater than 0.05, the linear regression models are adequate for the experimental data.

The precision of the method was evaluated by calculating the relative standard deviation (RSD) at several concentration levels of the compounds, and results are included in Table 3. RSD values were in general very homogeneous, lower than 10% for the intra-day precision (concentrations at 0.05, 0.10, 5, and 50 µg/mL), and lower than 5.6% for the inter-day precision (considering compound concentrations of 5 and 50 µg/mL).

Limits of detection (LOD) and quantification (LOQ), defined for a signal-to-noise ratio of 3 ($S/N=3$) and 10 ($S/N=10$), respectively, were estimated at the low nanogramme per millilitre for all the analytes (see Table 3).

In the development of the UAE method, a multivariate strategy of optimization was carried out with the aim of selecting the optimal working conditions. We studied the effect of four factors (each one at two levels) that might affect extraction efficiency: type of solvent, solvent volume, extraction temperature, and extraction time. The factors and levels considered, as well as the corresponding codes, are summarised in Table 4. For the optimization step, a real desiccant sample contaminated with DMF was employed. Since BT and TBP were not present in this sample, they were added to give a final concentration of 50 µg/g. In all experiments, the sample size was set at 50 mg (see sample preparation in the “Experimental” section). A 2^4 complete factorial design involving 16 experiments was employed.

This design has resolution V, which provides the advantage of being able to study main effects as well as two-factor interactions leaving five degrees of freedom to estimate experimental error. The experimental design data analysis was performed with the statistical software package Statgraphics Centurion XV (Manugistics, Rockville, MD, USA). The selected design allows to interpret the results using statistical tests and graphic tools in order to determine which factors and interactions have a statistically significant effect.

The analysis of the results obtained after running the 16 experiments produced the standardised Pareto charts showed in Fig. 1. The length of each bar in the graphs is proportional to the absolute value of its associated standardised effect. The standardised effect is obtained by dividing the estimated effect of each factor or interaction by its standard error. The effects are displayed in decreasing order of importance, which allows easy identification of the most important factors. The vertical dotted line in the graph represents the statistically significant value bound at the 95% confidence level. As can be seen in the figure, the most important factor for the extraction of BT and TBP was the type of solvent. Temperature was also significant for one compound, TBP, and was very close to the significance for the other species. Extraction time and solvent volume were not significant factors for the extraction of any of the target compounds. Interactions between factors were not significant in any case.

Figure 2 shows the main effect plots. This kind of plots shows the main effects with a line drawn between the low and the high level of the corresponding factors. The length of the lines is proportional to the effect magnitude of each factor, and the sign of the slope indicates the level of the factor that produces the highest response. As can be seen in the plots, the general tendencies were equivalent for all compounds. Regarding the significant factors, the most suitable solvent was ethyl acetate (the high level of this factor), and the most favourable extraction temperature was 25 °C (the low level of this factor). Solvent volume

Table 6 Concentration ($\mu\text{g/g}$) of the compounds in desiccant samples

Sample	DMF	BT	TBP
S1	n.d.	12.2	4.07
S2	120	6.63	4.97
S3	71.9	4.12	0.531
S4	136	1.29	n.d.
S5	1,460	16.3	n.d.
S6	2,640	2.64	0.713
S7	219	6.95	6.54
S8	530	0.243	0.501
S9	209	n.d.	n.d.
S10	710	4.42	3.61
S11	115	5.38	2.61
S12	n.d.	n.d.	n.d.
S13	3.57	n.d.	n.d.
S14	n.d.	n.d.	n.d.
S15	684	2.15	0.511
S16	3.70	1.80	0.592
S17	9.39	2.25	0.341
S18	100	2.69	0.346
S19	28.5	n.d.	0.147
S20	150	4.23	1.38
S21	151	n.d.	n.d.
S22	45.4	3.54	2.40
S23	62.4	1.93	0.119
S24	586	1.42	0.177
S25	223	1.11	0.187
S26	0.947	4.51	n.d.
S27	0.527	1.43	n.d.
S28	0.323	2.04	n.d.
S29	n.d.	11.1	0.739
S30	n.d.	32.4	n.d.
S31	n.d.	43.2	0.0528
S32	0.239	24.7	12.6
S33	n.d.	31.9	1.88
S34	3.52	71.8	0.602
S35	n.d.	11.1	n.d.
S36	n.d.	5.45	n.d.
S37	1.06×10^6	n.d.	n.d.

n.d. not detected (<LOD)

was not significant and thus, we selected 1 mL since it provides more concentrated extracts and lower solvent consumption. We decided to set the time at its lower level, 5 min, to achieve maximum sample throughput. In summary, the optimal UAE procedure involves the extraction of the samples at 25 °C with 1 mL ethyl acetate for 5 min.

Sample throughput would also improve if simultaneous extractions could be performed. Thus, we studied this possibility by performing six ($n=6$) simultaneous extractions in the selected conditions. The responses obtained as well as the RSD were identical to those obtained for single extractions (see Fig. 3). So, the feasibility of simultaneous extract up to six samples in only 5 min was demonstrated.

Some experiments were well carried out employing higher amounts of sample and lower extraction solvent volume. In the first case, aliquots of 200 and 500 mg of sample spiked at 100 $\mu\text{g/g}$ with the target compounds were extracted under the selected conditions, and the obtained responses were compared to those obtained using 50 mg sample. Results are depicted in Fig. 4a, in which, to facilitate the comparison, the responses obtained for 200 and 500-mg samples were divided by the expected increase factors (4 and 10, respectively) regarding the response for 50 mg. As can be seen, the analytes followed a similar behaviour, i.e. responses obtained using 200 and 500 mg sample were four- and tenfold higher than the ones obtained with 50 mg, respectively, demonstrating the method efficiency for extracting larger amounts of solid sample.

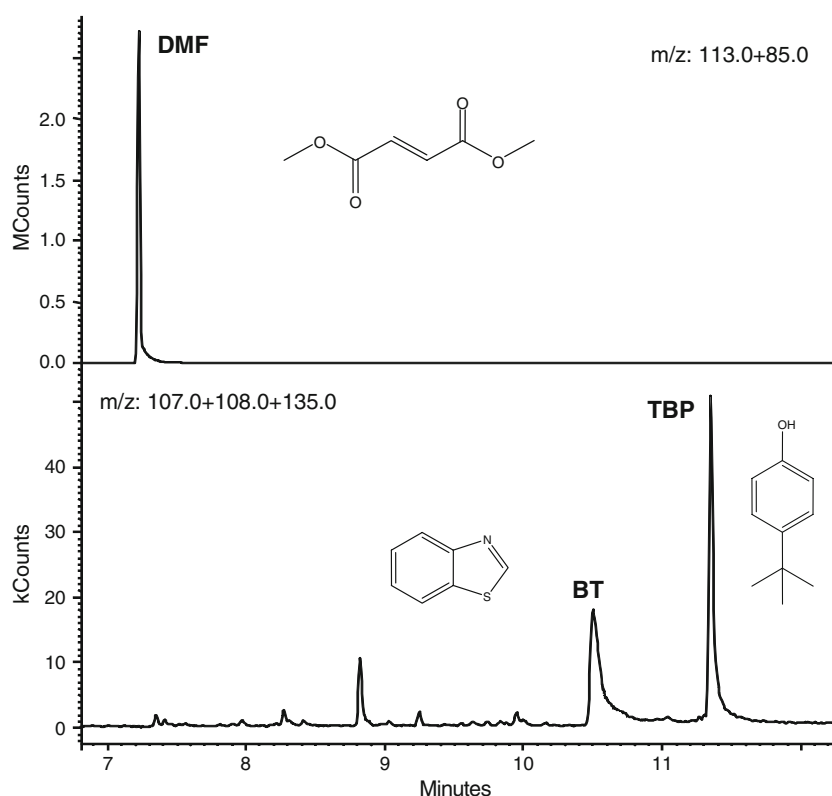
Additionally, the extraction with a lower volume of solvent (0.5 mL) was studied for sample amounts of 50 and 500 mg using a real sample containing the three target compounds at the low microgram per gramme level. Results showed that the obtained responses were twofold higher than those obtained using 1 mL (see Fig. 4b), thus indicating that the reduction in the extraction solvent volume could be useful if more sensitivity was eventually required.

Performance study and application of the method

Precision of the UAE-GC-MS experimental procedure was assessed using real samples spiked at four concentration levels (1, 10, 100 and 500 $\mu\text{g/g}$). Results showed low intra- and inter-day variations, with relative standard deviation (RSD) values about 5% and below 10% in all cases (see Table 5), thus equivalent to the ones obtained considering only the chromatographic analysis (see Table 3).

Limits of detection (LOD, $S/N=3$) and limits of quantification (LOQ, $S/N=10$), for the full UAE-GC-MS method were estimated using a non-spiked real desiccant sample (500 mg) containing the three compounds at relatively low concentrations (3.70, 1.80, and 0.590 $\mu\text{g/g}$ of DMF, BT and TBP, respectively). LOD and LOQ values are also presented in Table 5, and were found at the low nanogramme per gramme level. Therefore, the sensitivity of

Fig. 5 UAE-GC-MS extracted ion chromatograms obtained for a real desiccant sachet sample (S7)



the proposed method can be considered high, and make it suitable to determine DMF content in real samples [4].

Recovery studies were performed by applying the optimised method to the extraction of four desiccant samples spiked with the target analytes at different concentrations (1, 10, 100 and 500 $\mu\text{g/g}$). Previous analysis of these samples showed the presence of some of the compounds, and these initial concentrations were taken into account for calculating the recoveries. Results are depicted in Table 5, showing that recoveries were satisfactory for the three compounds at all concentration levels considered in the tested samples.

The method was finally applied to determine the levels of DMF, BT and TBP in sachets and tablets labelled as “mould proof agent”, “biochemical dry—desiccant”, “antimoulds—active mineral”, “desiccant—silica gel”, “silica gel” or just simply “do not eat” in the envelope. The samples presented different aspects (little balls, sand, and powder) and colours (colourless, white, grey, yellow). For the final determinations, some of the extracts were conveniently diluted. Results are summarised in Table 6. From the 37 samples tested, 27 contained DMF in concentrations ranging from 0.239 to

2640 $\mu\text{g/g}$, of which more than a half contained more than 100 $\mu\text{g/g}$ of DMF, and one of the samples, a “mould proof agent” tablet, was constituted by about 100% DMF. These results demonstrate that the content of the commonly found “desiccant” sachets and tablets in consumer products does not belong with the label of the desiccant, and hence, the high risk of exposition to this powerful allergen chemical through consumer goods. Only two samples were free of any of the target compounds, whereas all samples except five, contained BT in concentrations ranging from 0.243 to 71.8 $\mu\text{g/g}$; and more than half contained TBP at concentrations of 0.0528–12.6 $\mu\text{g/g}$. Figure 5 shows the extracted ion chromatograms of a sample containing the three target compounds (S7, see Table 6 for concentrations).

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