Simultaneous detection of five biocides in household products by gas chromatography-mass spectrometry

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Abstract: A gas chromatography-mass spectrometric method was developed for determining 5-chloro-2-methyl-4-isothiazolin-3-one (CMIT), 2-methyl-4-isothiazolin-3-one (MIT), 1,2-benzisothiazolin-3-one (BIT), 3-iodo-2-propynyl butyl carbamic acid (IPBC) and benzoic acid (BA) in household products. A 0.5 g sample was placed in a test tube and dissolved with 5 mL water, 5 mL methylene chloride and 1.0 mL methanol. The solution was extracted by ultra-sonication followed by mechanical shaking using the salting out effect. Under the established condition, the lowest quantification limits of all analytes were in the range of 0.04-10 mg/kg and their relative standard deviations were less than 8.0 %. The method was used to analyze 10 household products. As a result of analyzing 10 household products, MIT was detected in the range of 1.2-3.5 mg/kg in 3 of 10 samples, CMIT was detected in the range of 2.6-8.2 mg/kg in 3 of 10 samples, and BA was detected in the range of 5.0-15 mg/kg in 4 of 10 samples. Meanwhile, BIT and IPBC were not detected in any of the products. It has been shown that this method can be used for the simultaneous determination of biocides with various physical and chemical properties in household products.

Key words: biocides, household products, ultra-sonication, gas chromatography-mass spectrometry

1. Introduction

Biocides are defined as substances and preparations that exert the effect of destroying, inhibiting, preventing or controlling harmful organisms by chemical or biological means according to Biocidal Products Directive 98/8/EC.[1]

Among them, isothiazol-3-ones have been extensively used as biocides in various industrial water treatment applications to control microbial growth and biocontamination due to their excellent antifungal and antibacterial properties.[2,3] They have also been used as preservatives to prevent fungal growth in a wide range of manufactured products such as adhesives, paints, varnishes and natural and artificial leather.[2] The most frequently used isothiazolinones are methylisothiazolinone (MIT), methylchloroisothiazolinone (CMIT) and benzisothiazolinone (BIT), and a mixture

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of CMIT and MIT (3:1). BIT is prohibited for use in cosmetics,[3] but it has been generally used as cleaning products[3] and leather products.[4] 3-Iodo-2-propynyl butyl carbamic acid (IPBC) is a disinfectant/antimicrobial agent used as a preservative in paints, adhesives, emulsions, metal cutting oils, oil recovery drilling mud/packer fluids, plastics, textiles, inks, paper coatings and wood products. IPBC is also applied to heating, ventilation and air conditioning ducts and equipment to control mold and fungi.[5] Benzoic acid (BA) is used as a food preservative and is best suited for foods, fruit juices and soft drinks that are naturally in the acidic pH range. Its use is regulated as a preservative in food, beverages, toothpaste, mouthwash, cosmetics and pharmaceuticals.[6] With the increasing use of these biocides, concerns have been reported regarding hypersensitivity and allergic contact dermatitis by both workers and consumers.[5-7]

In particular, as severe lung disease has been prevalent in Korea since 2006, lung toxicity of CMIT and MIT along with polyhexamethylene guanidine has been confirmed, raising the problem of continued use in household products. The European Union restricts the maximum level of CMIT and MIT in personal care and cosmetic products to 15 mg/kg.[8] If there is a method that can simultaneously analyze biocides with various chemical functional groups such as carbamates, acids, and thiazoles, it would be very helpful to regulate and control biocides.

A number of analytical procedures have been proposed for the determination of biocides in commercial products, which contain a wide range of highly complex matrices that can make significant analytical difficulties. Adequate sample preparation is therefore an important aspect of quantitation of biocides in consumer products. The most common and widely applied sample preparation techniques include liquid-liquid extraction (LLE),[9,10] solid phase extraction (SPE)[10-12] and ultrasonic assisted extraction (UAE).[11,13-15] LLE is inexpensive and flexible because it allows parallel preparation of multiple samples in sample preparation for purification and concentration of biocides in matrix.[9,10] SPE has the advantages of high recovery, solving emulsion problems, reducing

the amount of organic solvent used, and requiring a small amount of sample. A variety of SPE stationary phases have been used for biocide analysis.[10,11] Furthermore, solid-phase microextraction (SPME) technology can overcome the disadvantages caused by sample matrix interference.[12] UAE is an effective alternative to conventional sample preparation methods for solid and liquid samples with high density and viscosity.[11,13-15]

Until now, most methodologies for measuring biocides in household products involve the use of liquid chromatography (LC) or high-performance liquid chromatography (HPLC),[9,11-20] but to a lesser extent gas chromatography (GC).[10] Methods based on LC or HPLC are most commonly used for the analysis of biocides. Detection is carried out by diode array (DAD),[14-18] simple quadrupole mass spectrometry (MS),[11,13] triple quadrupole mass spectrometry (MS/MS).[9,12,14,19,20] In general, MS/MS detectors provide high sensitivity and selectivity to reduce matrix interference. On the other hand, the use of GC does not show good performance for biocides analysis.[10] In particular, BIT, carbamates, and organic acid require derivatization to improve chromatographic performance. However, the original performance of GC-MS is excellent in selectivity and sensitivity, so if the analysis conditions are well established, it is judged to be a useful equipment for the analysis of biocides. *Table* 1 summarizes the analytical methods reported in the literature for the determination of isothiazolinone biocides in different samples.

This paper describes UAE to detect 5 biocides in household products combined with analysis by gas chromatography-mass spectrometry-selected ion monitoring (GC-MS-SIM). This paper focuses on the validation of sample preparation and detection methodology. The developed method was used to determine 5 biocides in household products.

2. Experimental

2.1. Chemicals and reagents
MIT, CMIT, BIT, IPBC, BA and 2-acetyl-2-thiazoline (internal standard) were purchased from Sigma-

Aldrich (USA). Analytical grade sodium chloride, methylene chloride, acetone and methanol were from J. T. Baker (USA). Water was purified by Milli-Q equipment (Millipore Corp., Milford, MA, USA).

2.2. Collection of household product samples

The household product samples were purchased from a local supermarket or internet shopping mall in the Republic of Korea. Samples were made in Republic of Korea and China. All samples were analyzed within three months of purchase after storage in a refrigerator.

2.3. Ultrasound-assisted cloudy extraction

UAE method was used to extract biocides in household product samples. After transferring 0.5 g of sample to a 15-mL glass test tube, 5.0 mL of pure water, 5.0 mL of methylene chloride and 1.0 mL methanol were added to the sample. The solution was extracted by ultra sonication for 30 min. 2.0 g sodium sulfate and 50 μL of internal standard (10 mg/L in methanol) were placed in the sample solution. After mechanical shaking for 10 min and centrifugation for 5 min, the organic layer was concentrated to 100 μL under a stream of nitrogen. The solution was transferred to a V-shaped automatic vial, and 2.0 μL of the solution was injected into the GC-MS system.

Samples in which analytes were not detected were selected as a control sample and the control sample was used for the method validation.

Calibration curves were established by extraction after adding 0, 0.02, 0.05, 0.2, 0.5, 1.0, 2.0, 5.0 and 10.0 μg of analytes to 0.5 g of a control sample. The corresponding concentrations of the standards were 0, 0.04, 0.1, 0.4, 1.0, 2.0, 4.0, 10.0 and 20.0 mg/kg. The ratios of the peak areas of the standards to that of the internal standard were used to quantify the analytes. The lowest limit of detection (LOD) and limit of quantification (LOQ) were determined as the lowest concentration of the standard solution resulting in a signal-to-noise ratio of 3:1 and 10:1.

2.4. GC-MS

The gas chromatograph used was an Agilent 7890

A with a split/splitless injector (Agilent Technologies, Santa Clara, CA, USA). The analytical column was a 60 m HP-5 MS column (cross-linked 5 % phenylmethylsilicon, 0.25 mm I.D. × 0.25 μm df). The flow rate of helium as a carrier gas was 1.0 mL/min. The injector temperature was set at 280 $^{\circ}$C. The oven temperature program began at 80 $^{\circ}$C (held for 1 min), raised to 310 $^{\circ}$C at 10 $^{\circ}$C/min (held for 10 min). All mass spectra were obtained with an Agilent 5975 B instrument (Agilent Technologies, Santa Clara, CA, USA). The ion source was operated in the electron ionization mode (EI; 70 eV, 230 $^{\circ}$C). Full-scan mass spectra (*m/z* 35-400) were recorded for the identification of analytes at a high concentration. Confirmation of trace chemicals was completed by three MS characteristic ions and the ratio of the three MS characteristic ions, and the GC-retention time matched the known standard compound. The ions selected in this study were as shown in *Table* 2.

3. Results and Discussion

3.1. Optimization of the analytical method

So far, the simultaneous analysis of five biocides with chemically diverse properties has been separated by LC or HPLC, as shown in *Table* 1. In this study, a GC-MS method that can simultaneously and sensitively measure theses five biocides was developed. In order to analyze water-soluble analytes, including benzoic acid, contained in household chemical products by GC-MS, the analytes must be extracted to organic solvent from the sample to obtain a final solution that does not contain water. In addition, it is necessary to find GC conditions with symmetric, sharp, and quantitative peak shapes, and to establish MS conditions through ion selection with high sensitivity.

Initially, we tested direct extraction of analytes from household products using chloroform, methylene chloride, acetonitrile and methanol to achieve optimal extraction conditions. As a result, high extraction efficiency close to 100 % was obtained with all organic solvents for 5 biocides, but matrix interference was very severe. Therefore, it was determined that the turbid extraction method was suitable for achieving

Table 1. Comparison of analytical method for determination of biocides in household products and their analytical results

Ref	Analyte	Matrix	Sample preparation	Instrumental Measurement	LOD (mg/kg)	LOQ (mg/kg)	Accuracy (%)	Detection conc range (mg/kg)
9	MIT CMIT BIT OIT	Paints	LLE[a]	UPLC-MS/MS	Not available	Not available	Not available	1.02-357.89 / 8.23-13.05 / 28.60-1110.74 / ND
10	MIT CMIT BIT OIT	Adhesives	LLE[a], SPE[b] (Different extraction solvents and solid adsorbents were used for each analyte)	GC-FPD GC-MS (for identification)	0.005-0.050 mg/L (as standard solution)	Not available	Not available	4.4-10.4 / 13.7-26.5 / ND / 5.9-133.0
11	MIT CMIT BIT OIT IPBC	Consumer products	UAE[c]	HPLC-MS	0.011-1.6	Not available	60.4-113	0.03-70.2 / ND-11.3 / 9.9 (Mean) / 0.096 (Mean) / 0.58 (Mean)
12	MIT CMIT BIT OIT	Cosmetics Household products	MSPD[d]	HPLC-MS/MS		0.0066-0.06	Not available	1.18-2.90 / 4.19-8.44 / 116-377 / 0.35-1.21
13	MIT CMIT BIT OIT	Detergents Cosmetics	UAE[c]	LC-MS	0.94-2.03	1.3-3.8	52-147	4.3-10.0 / 6.0-279.3 / 23.4-186.2 / 7.9
14	MIT CMIT BIT OIT	Food packaging	UAE[c]	UPLC-MS/MS	0.001-0.01	0.002 to 0.020	81.3-103.4	Not available
15	MIT CMIT	Cosmetics	UAE[c]	UPLC-DAD	0.175-0.35 mg/L (as standard solution)	Not available	Not available	Not available
16	MIT CMIT	Adhesives	HF-LPME[e]	HPLC-DAD UHPLC-Q-TOF-MS(for identification)	0.037-0.147	0.12-0.49	Not available	49.2-57.78 / 9.85-11.80
17	MIT CMIT Sodium benzoate	Cosmetics Cleaning agents Pharmaceuticals	UAE[c]	UPLC-DAD	0.08-4.38 (as standard solution)	0.24-13.15 (as standard solution)	87.77-113.63	1.21-8.91 / 1.62-297.28 / 0.74-1635.09
18	MIT CMIT	Cosmetic products	UAE[c]	HPLC-DAD	0.005-0.025 (as standard solution)	Not available	Not available	2.1-5.7 / 3.8-10.9
19	MIT CIMT BIT OIT	Adhesive	Vortex extraction	HPLC-MS/MS	0.002-0.01	Not available	81.5-101.5	12.94-60.79 / 3.28-28.36 / 2.27-123.5 / ND
20	MIT CMIT	Cosmetic products	Mechanical shaking	UPLC-MS/MS	0.01	0.02	90-110	0.393-89.6 / 0.260-10.3
This study	MIT CMIT BIT IPBC BA	Household products	UAE[c]	GC-MS	0.32 / 0.08 / 1.0 / 0.04 / 10	0.11 / 0.26 / 3.3 / 0.13 / 3.3	96.0-110	1.0-3.0 / 2.0-8.0 / ND / ND / 5.0-15

LLE[a], liquid–liquid extraction; SPE[b], solid-phase extraction; UAE[c], ultrasonic-assisted extraction; MSPD[d], matrix solid-phase dispersion; HF-LPME[e], three-phase hollow-fiber liquid-phase microextraction.

optimal extraction conditions for multiple analytes with strong and weak water solubility. Cloudy extraction is a method of extracting an analyte using an extraction solvent and a dispersion solvent at the same time, and a turbid solution is formed as a microemulsion in which the extraction solvent is dispersed in an aqueous solution sample. In a turbid solution, the contact surface between the sample and the extraction solvent is dramatically improved due to the formation of a microemulsion, after which equilibration is achieved very quickly, thereby improving the extraction efficiency of the target analyte.

To test optimal extraction conditions, four solvent pairs were tested using methylene chloride and ethyl acetate as extraction solvents, and methanol and acetone as dispersion solvents. To increase the extraction efficiency, an excess of salt was added to give a salting-out effect. As a result, the method of using methylene chloride as an extraction solvent, methanol as a dispersion solvent, and pure water for purification purposes at the same time was a very efficient extraction method for the analysis of biocides in household products. Spike samples were prepared at two different concentrations for 5 analytes and recovery was calculated as the percentage of analyte recovered.

The recovery of the biocide in the household product samples was greater than 57 %, as shown in *Table* 2. The recoveries of biocides from household products were 57-59 % for MIT, 76-82 % for BIT, and nearly 100 % for other biocides. Because MIT has very high water solubility, the extraction efficiency by LLE is generally low at 20-30 %, but the extraction efficiency was improved to 57 % by combining cloudy extraction using ultrasonication and mechanical extraction using salting-out effect.

For GC separation of five biocides including benzoic acid, the use of semipolar stationary phases such as Wax or InnoWax was initially attempted, but BIT and IPBC could not be analyzed at the column temperature upper limit of 260 $^{\circ}$C. Therefore, HP-5MS column, a non-polar stationary phase with the column temperature upper limit of 350 $^{\circ}$C was used for GC separation of five biocides, and all analytes fortunately showed sharp peaks. For accurate quantification, the internal standard method was used, and it was quantified as the ratio of the area of each peak to the area of the internal standard. After adding the analytes to the control sample, extraction was performed, and as a result of analysis by GC-MS, no additional peaks or interference peaks were observed near the retention
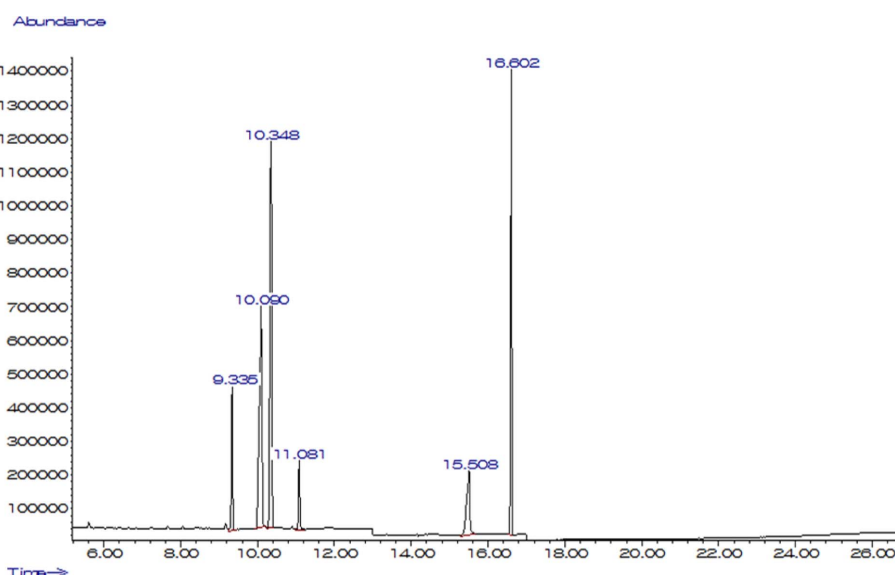

Fig. 1. GC-MS SIM chromatogram of the extract from household product spiked in the concentration of 0.5 mg/kg (Internal standard: 9.335 min, benzoic acid: 10.090 min, MIT: 10.348 min, CMIT: 11.081 min, BIT: 15.508 min, IPBC: 16.602 min).

Table 2. Validation results for the analysis of biocides in household chemicals

No	Compound	Chemical Formula	CAS Number	Molar mass (g/mol)	Quantification ion (m/z)	Qualification ions (m/z)	Korea EPA LOQ (mg/kg)	Detection limit (mg/kg) LOD	LOQ	Detection range	Calibration curve Linear equation	r	Spiked Conc (mg/kg)	Recovery (%), (n=5) Mean±SD	%RSD	Precision and accuracy (mg/kg) (n=5) Mean±SD	Accuracy (%)	%RSD
1	MIT	C_4H_5NOS	2682-20-4	115.1	115	58, 87	5.0	0.32	0.94	0.5-50	y=0.0026x-0.0074	0.9989	5.0	59.3±1.7	2.92	5.0±0.1	100	2.00
													10.0	57.4±4.8	8.40	10.4±0.7	104	6.73
2	CMIT	C_4H_4ClNOS	26172-55-4	149.6	149	57, 85	5.0	0.08	0.24	0.1-50	y=0.0004x-0.0032	0.9995	10.0	109±6.4	5.87	10.2±0.6	102	5.88
													15.0	110±8.2	7.45	16.5±0.7	110	4.67
3	BIT	C_7H_5NOS	2634-33-5	151.2	151	96, 123	5.0	1.0	3.0	1.0-50	y=0.0065x-0.1155	0.9954	2.50	82.4±6.6	8.06	2.4±0.2	96.0	8.00
													5.0	76.0±6.5	8.53	5.2±0.3	104	6.00
4	IPBC	$C_8H_{12}INO_2$	55406-53-6	281.1	165	182, 57	1.0	0.04	0.12	0.05-100	y=0.0075x-0.1817	0.9964	10.0	92.2±2.2	2.35	10.3±0.1	103	1.00
													100	103±5.3	5.10	97.7±2.4	97.7	2.40
5	Benzoic acid	$C_7H_6O_2$	65-85-0	122.1	105	122, 77	50	10	31	10-100	y=0.0076x-0.3586	0.9996	25	97.9±3.9	3.94	26.4±0.8	106	3.20
													50	106±9.3	8.82	54.4±3.1	109	6.20

time of the analyte as shown in *Fig*. 1.

The selective ion monitoring (SIM) is effective in eliminating interfering substances. If possible, ions with high abundance were selected for high sensitivity and high mass (m/z) ions were selected for high selectivity. Molecular ions $[M]^+$ from MIT, CMIT, BIT and internal standard were dominant and therefore these ions were selected as quantitative ions. The fragmentation of IPBC and BA was dominated by ions generated by the cleavage of [I] and [OH] from each molecular ion, and these ions were selected as quantitative ions as shown in *Table* 2.

3.2. Validation
3.2.1. Detection limits
The lower limit of detection (LOD) and lower limit of quantification (LOQ) were calculated with signal-to-noise ratios of 3:1 and 10:1 as described in Experimental. The LOD and LOQ in this study was shown in *Table* 2. In any case, the areas observed for these compounds in blank water are always smaller than those corresponding to the LOD, and thus, it can be assured that the carryover is less than the LODs of all analytes. In comparing our LODs and LOQs with those of methods using HPLC-DAD[15-18] or LC-MS,[11,13] our LODs and LOQs were less than or similar to those reported by most literature. On the other hand, the LODs and LOQs of our method, excluding BA, were up to 100 times higher than the previously reported those in the method using the expensive instrument LC-MS/MS.[12,14,19] Although LODs of isothiazolinones in our method are much higher than those of LC-MS/MS, it is a valuable analytical method in that it analyzes simultaneously with BA. The Korean Ministry of Environment limits the highest levels of 15 mg/kg (MIT), 100 mg/kg (CMIT), 500 mg/kg (BIT), 1,000 mg/kg (IPBC) and 5,000 mg/kg (BA) in fabric softener.[21] Otherwise, the European Union restricts the maximum levels of CMIT and MIT 15 mg/kg in personal care and cosmetic products.[8] The LOQs of our analytical method were at least 1/15 lower than their maximum levels of the Korean Ministry of Environment[21] and the European Union.

3.2.2. Calibration curve and linearity
The standard curve was obtained by computing the regression line of the peak area ratios of the analytes versus concentration using a least-squares fit and demonstrates a linear relationship. The calibration curves were linear in two to four orders of magnitude with correlation coefficients higher than 0.99 in all cases. The line of best fits for biocides are as described in *Table* 2.

3.2.3. Precision and Accuracy
The reproducibility of the assay was very good. For five independent determinations in the two different concentration, the accuracy was in the range of 96.0-110 %, and the precision was less than 8.0 % (*Table* 2). It can be seen that the accuracy of the method developed in this study is superior to those of other methods as shown in *Table* 2.

3.3. Household products analysis
We used the proposed method to analyze the target biocides in ten household products. As a result of analyzing biocides, MIT was detected in the range of 1.2-3.5 mg/kg in 3 of 10 samples, CMIT was detected in the range of 2.6-8.2 mg/kg in 3 of 10 samples, and benzoic acid was detected in the range of 5.0-15 mg/kg in 4 of 10 samples. They are mainly detected in children's toy products made in China, so a more detailed investigation is needed for children's toys.

4. Conclusions

In this paper, we tried to combine cloudy extraction using ultrasonication and mechanical extraction using salting-out effect for the detection of biocides in household products. The recoveries of biocides were greatly improved, many interfering substances were removed. The peaks of biocides showed good chromatographic properties and a sensitive response for the EI-MS (SIM).

The major advantages of this method are described as follows: 1) The method allows simultaneous determination of trace levels of MIT, CMIT, BIT, IPBC and BA in household products. 2) Although

this method requires only a small amount of 0.5 g, the LODs determined by this study were less than or similar to the previously reported LOD values using HPLC or GC-MS. 3) The cloudy extraction method developed in this study is simple and fast, and therefore, it can be easily applied to many household product analyses.

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