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Identification and Determination of Methylisothiazolinone and Chloromethylisothiazolinone in Cosmetics by Liquid Chromatography Tandem Mass Spectrometry

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ABSTRACT

Isothiazolinone is a broad-spectrum preservative that is widely used in household products to prevent the growth of bacteria, mold, and yeast. Methylisothiazolinone (MIT) and chloromethylisothiazolinone (CMIT) are two derivatives of isothiazolinones that are commonly used in cosmetics. Recently, numerous studies have reported that these compounds may cause eczema, edema, or allergic reactions when used in higher concentrations or as leave-on products. The Indonesian FDA stated that MIT and CMIT are prohibited for use in leave-on cosmetics products. Therefore, this study evaluated whether cosmetics in the Indonesian market are free from MIT and CMIT. A method for the analysis of MIT alone and an MIT/CMIT mixture using liquid chromatography equipped with tandem mass spectrometry quadrupole time of flight was developed and validated in this study. This was followed by the determination of the MIT and CMIT content in various cosmetic products. For this determination, the multiple reaction monitoring was adjusted to m/z 116.0165 $[M+H]^+$ for MIT and set to m/z of 99.0091, 101.0215, and 84.9954 for the detection of the transition ion of MIT. Meanwhile, for CMIT, this was set to m/z 149.9775 $[M+H]^+$ and to m/z at 134.9977, 86.9906, and 115.0447 for the detection of the transition ion signal of CMIT. The results showed that the retention times of MIT and CMIT were 4.53 and 5.25 min, respectively. Several parameters of the method validation, including specificity, linearity, recovery, stability, precision, accuracy, determination of the detection limit and quantitation limit, were measured, and the results met the validation requirements. The developed method was then applied for the detection of MIT and CMIT in 21 cosmetic products, including soaps, shampoos, lotions, lipstick, and liquid cosmetics that were obtained from local markets and pharmacies. MIT and CMIT were detected in three samples, either as a single inclusion or as a mixture. It can be concluded that cosmetics in the Indonesian market are not yet free from MIT and CMIT.

Keywords: cosmetic products, chloromethylisothiazolinone, methyl-isothiazolinone, LCMS/MS QTOF, preservatives

INTRODUCTION

Preservatives are typically added by manufacturers to avoid product deterioration, as they may be easily contaminated by microorganisms, especially products with a high water content. The isothiazolinone preservative group, particularly methylisothiazolinone (MIT) and chloromethylisothiazolinone (CMIT), is frequently used in cosmetic products because it exhibits strong broad-spectrum antimicrobial activity at low concentrations (Tomas *et al*., 2020). The IUPAC names of MIT and CMIT (Fig. 1a) are 2-methyl-4-isothiazolin-3-one and 5-chloro-2-methyl-4-isothiazolin-3-one, respectively. They can be used individually or as an MIT/CMIT combination. On the market, a combination of CMIT and MIT at a 1:3 proportion is commercially available and is known under the brand name Kathon CG (cosmetic grade) (Alanazi *et al.*, 2022 and Burnett *et al.*, 2010). Some cosmetic

preparations that frequently contain MIT or CMIT are rinse-off products (shampoos and conditioners) and leave-on products (creams, gels, tonics, eyeshadows, nail polishes, lipsticks, and lotions) (Prapurandina *et al.*, 2021 and Wittenberg *et al*., 2015). The MIT and CMIT compounds have been described to diffuse across the bacterial cell membrane and fungal cell wall. In the intracellular media, the electron-deficient sulfur of these compounds' N–S bond can react with the nucleophilic groups of the cellular components, such as the thiols from cysteines at the active sites of proteins, thereby blocking their enzymatic activity and ultimately inducing cellular death. MIT and CMIT can quickly combine with thiol-containing substances, such as cysteine and glutathione (GSH), to generate disulfide derivatives that trigger a cascade of reactions that impact essential cellular processes (U.S. EPA, 2020) (Figure 1b). These reactions can impede cellular growth within minutes or cause cell death within hours (Ducup de Saint Paul, 2021).

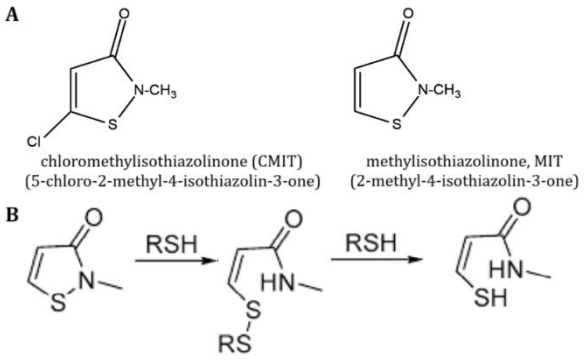

Figure 1. Chemical structure of chloromethyl-isothiazolinone (CMIT) and methylisothiazolinone (MIT) (a) metabolism pathway of isothiazoli-nones and thiols from cellular components (e.g., glutathione) (b).

In recent years, it has been revealed that the use of MIT and CMIT can cause skin sensitivity and allergic reactions in some individuals, especially when used at high concentrations or as leave-on products. Therefore, regulatory bodies such as the European Union (EU) have imposed restrictions on their use. MIT is no longer permitted in products that do not require application in the EU and is only permitted at certain concentrations in products that can be rinsed off (Burnett *et al*., 2021). In Indonesia, the Regulation of the Food and Drug Supervisory Agency of the Republic of Indonesia Number 17 of 2022 stated that MIT is prohibited from being added in leave-on cosmetics. They are permitted only for rinse-off preparations with a maximum concentration of 0.0015% and 0.001% for the MIT/CMIT combination and single MIT, respectively (Baranowska *et al.*, 2015 and Indonesian FDA, 2022). Cosmetic manufacturers, factories, and distributors must comply with this regulation. Meanwhile, the Indonesian FDA is obliged to supervise cosmetics circulating in the market. To ensure that the use of MIT and CMIT is safe, a validated analysis method is needed to measure the content of MIT and CMIT in cosmetics. Several analytical methods have been conducted, including MIT and CMIT analysis in personal care products using HPLC with dual detection (diode-array and fluorescence), by Abad-Gil *et al*. (2021). Moreover, analysis using LCMS/MS has been applied to measure MIT and CMIT in household products, food, cosmetics, and rat blood plasma. Heo *et al*. (2018) developed an analysis method using methanol as the mobile phase. The results revealed that the analysis time was still too long, about 35 min for one run in the chromatography system. Therefore, the method needs to be modified to optimize the analysis time efficiency (Heo *et al*., 2018; Zhong *et al*., 2019; Kim *et al*., 2018; Baranowska *et al*., 2015; Ducup de Saint Paul *et al*., 2021). In addition, Prapurandina *et al*. (2021) reported that MIT and CMIT in cosmetic products can be detected using GC-MS-MSPD.

Research on the use of MIT and CMIT in cosmetics circulating in the Indonesian market (especially in Jakarta and its surroundings) has not been previously performed. Therefore, this study used an analysis method that has previously been developed with modifications to investigate these circulating cosmetics. Based on the results of this study, the use of MIT and CMIT in cosmetics that are available in the market can be determined. Furthermore, the compliance of the cosmetic industry in implementing related regulations can be established.

MATERIALS AND METHODS

Chemicals and reagents

LCMS grade water, methanol, and acetonitrile were acquired from Merck (Darmstadt, Germany). MIT (CAS: 2682-20-4) was obtained from the Indonesia Pharmacopeia Standard (BPFI), CMIT (CAS: 26172-55-4) was purchased from Ehrenstorfer (Augsburg, Germany), and Leucine Enkephalin ($C_{28}H_{37}N_5O_7$) was obtained from Waters (Milford, MA, USA). A total of 24 cosmetic samples were collected, which consisted of 10

shampoos and conditioners, three liquid soaps, three soap bars (one of which was a baby soap), and eight other leave-on products, such as lipstick, eyeshadow, feminine care products, face cream, body lotion, face toner, and nail polish. All samples were manufactured in Indonesia and it was stated on the label that they contained MIT.

Instruments

An ACQUITY UPLC® I-Class equipped with a binary solvent manager and a quaternary pump that has a maximum operating backpressure of 15000 psi was used to perform the LC (Waters, Milford, MA). Throughout the operation, the sample manager was set to 10°C. An Acquity UPLC C18 HSS T3 column (1.8 µm, 2.1 i.d. × 100 mm, Waters) was used to perform the separations.

The sample manager and column temperature were set to 10°C and 40°C. The LC was then coupled with a Xevo® G2-XS QTOF Mass Spectrometer (Waters). System control used the UNIFI™ Workstation ver 1.9.3 scientific information system, which managed UPLC-MS/MS operation, data acquisition, quantitation, and report generation. Electrospray ionization-positive mode was selected. The ion spray was set at 2500 V. Analyzer mode was optimized for high sensitivity by adjusting gas flow, capillary voltage, sample cone, desolvation temperature, MRM, and collision energy conditions. The capillary voltage was 3.0 kV, and the sample cone was 40 V. Source and desolvation temperatures were 140°C and 550°C. Gas flow was 10 L/h, and desolvation gas flow was 880 L/h. For MIT detection, the parent ion and three product ions were m/z 116.0165, 99.0091, 101.0215, and 84.9954. For CMIT detection, the parent ion was m/z 149.9775 and fragment ions were m/z 134.9977, 86.9906, and 115.0447.

Preparation of the standard solutions

The standard solution was prepared by dissolving a single MIT standard as well as the MIT/CMIT mixture standard in methanol for a final concentration of 750 ng/mL.

Preparation of the sample and spiked sample solutions

The sample solution was made by weighing 0.5 g of the sample and placing it into a 15 mL centrifuge tube. It was then completely dissolved with 10 mL of the solvent and filtered using a 0.2 µm PTFE membrane filter. The spiked sample solution was made by adding 0.4 mL of the standard solution to the final concentration of 750 ng/mL (International Conference on Harmonization (ICH), 2005 and U.S. Pharmacopeia, 2021).

Method optimization

By adjusting the mobile phase composition, injection volume, and flow rate, the chromatographic conditions were optimized. The retention time (Rt), peak shape, tailing factor, and highest resolution (Rs) >1.5 are some parameters that define the ideal conditions for chromatography analysis.

Mobile phase composition

The mobile phase consisted of a 0.1% formic acid solution in water as mobile phase A and a 0.1% formic acid solution in acetonitrile (MeCN) as mobile phase B. A gradient elution program was used by gradually changing the composition of the mobile phase over time (Table I).

Table I. UPLC gradient setting

	Time (Min)	Mobile Phase A (%)	Mobile Phase B (%)	Curve
Condition 1	0.00	100	0	Initial
	2.00	30	70	6
	5.00	30	70	6
	5.10	100	0	6
	7.00	100	0	6
Condition 2	0.00	100	0	Initial
	2.00	100	0	6
	4.00	60	40	6
	4.10	100	0	6
	5.00	0	100	6
	5.10	100	0	6
	7.00	100	0	6

Injection volume

The injection volume was optimized for 15, 10, and 5 µL.

Flow rate

The flow rate of the mobile phase was optimized in the 0.7–1.0 mL/min range to obtain maximum separation performance. Moreover, the mobile phase was sonicated for 10 min before use in chromatography.

Method validation

This method was validated according to the ICH and AOAC criteria, which included specificity,

linearity, matrix effect, accuracy, repeatability (intra-day precision), limit of detection (LOD), and limit of quantitation (LOQ). To evaluate specificity, MIT and CMIT peaks were observed to ensure they could be separated from each other and from the sample matrix signal. For linearity assessment, calibration standard curves were prepared in the range of 375–1125 µg/mL for MIT. The MIT/CMIT mixture was prepared at a 1:3 concentration ratio. To match conditions, the linearity curve was also prepared in a blank matrix extracted at the same concentration range as the calibration standard curve. Accuracy was evaluated by adding the standard to blank samples, with recovery studies performed at three different standard concentrations.

System suitability test

The system suitability test (SST) procedure was performed using six injections of a single MIT standard solution and a MIT/CMIT mixture, each using the same concentration of 750 ng/mL. Thereafter, the relative standard deviation (RSD) of time and area (AOAC International, 2016; ICH, 2005) was calculated.

Specificity and selectivity

Multiple injections of a mixture standard solution of MIT and CMIT and the sample solution from various matrices were used to determine the specificity and selectivity. Measurements of specificity and selectivity were performed to demonstrate that a single MIT and CMIT peak can be separated with a minimum resolution of 1.5 (AOAC International, 2016; ICH, 2005).

Linearity

Linearity refers to the linearity of the relationship between the concentration and area. The ICH guidelines recommend that to establish linearity, a minimum of five standard concentrations are required. In this study, linearity was determined at five concentrations of the spiked sample series with two replicates. The acceptance criteria for the linearity parameters were the correlation value ($r > 0.999$) and the variance of the intercept ($V_{x0} < 5\%$) (AOAC International, 2016; ICH, 2005).

Repeatability (intra-day precision)

The precision of an analytical method refers to the closeness of agreement between independent test results under specified conditions. This indicates the consistency and reproducibility of the method. It is an essential parameter for assessing its reliability. Precision is usually expressed as the standard deviation (SD) or %RSD (also known as the coefficient of variation) of a series of measurements. Three replicates of three spiked sample concentration series were injected to calculate the repeatability (intra-day precision) followed by RSD calculation (AOAC International, 2016; ICH, 2005; Gimeno *et al*., 2016).

Accuracy

The accuracy of an analytical procedure is the closeness of the test results obtained from that procedure to the true value. The accuracy of an analytical procedure should be established across its analytical range. In this study, the accuracy was established using three concentration series, each with three replicates. This was followed by recovery calculations (AOAC International, 2016; ICH, 2005).

Determination of the LOD and LOQ

LOD is the smallest concentration of analyte that can be detected using the method. Meanwhile, LOQ is the smallest concentration that can be quantitatively calculated using the method. A series of mixed standard solutions were injected, and their concentrations were measured at 0.5, 1, 2, 3, 4, and 5 ng/mL. A calibration curve was then prepared, and the gradient (b) as well as the SD of the intercept (SA) were calculated. The LOD value ($3 \times SA/b$) and LOQ ($10 \times SA/b$) were obtained by extrapolation.

Commercial sample analysis

The validated LCMS/MS method was applied to determine the MIT and CMIT preservatives in the various personal care and cosmetic products. These products included solid samples (face powder and eyeshadow), semisolid samples (liquid and bar soap, shampoo, lotion, and cream), and liquid samples (facial toner). All 24 samples were purchased and randomly selected from a local supermarket and stored at room temperature. The complexity of the sample matrix determined how the samples were prepared.

RESULTS AND DISCUSSION

A liquid chromatograph (Acquity, Waters) interfaced with a quadrupole time-of-flight mass spectrometer was used to develop the UPLC-MS/MS method. Both the optimization and validation analyses were performed using the

positive ionization mode. The method validation refers to the USP 40 and ICH Q2 (R1) Guidelines, which require specificity, precision, accuracy, and determination of LOD and LOQ for both identification and determination purposes (ICH, 2005; U.S. Pharmacopeia, 2021).

Optimization of the chromatographic and mass spectrometric conditions

A chromatographic technique was created to quickly and simultaneously identify two isothiazolinone compounds in a range of consumer products. Under this study's chromatographic conditions, the total ionic chromatograms (TIC) showed distinct peaks and well-defined separations. To achieve these results, the chromatographic conditions were optimized by adjusting the extraction method, dilution solvent, and settings of the gradient program. The extraction process length and pretreatment parameters were examined to improve efficiency. Vortex and ultrasonic extractions are frequently used because they are simple and effective for extracting organic molecules. To find the best extraction solvent, an experiment compared the extraction efficiency using 60% methanol and 100% methanol. The procedure was as follows: weigh 0.5 g of cosmetic sample, extract with 10 mL methanol, ultrasonicate at 1500 W, and vortex at 4500 rpm for 10 min until completely dissolved. Vortex and ultrasonication were selected because they use practical resources generally found in a laboratory. This aligns with Zhong et al. (2019), who reported that analyte concentration is significantly affected by physical step duration. Based on the results, dissolving the sample in 100% methanol yields the optimal amount of analyte extracted and minimal co-extractant. This extraction method is simple and has few steps, so it can be easily applied by other laboratories. To prove robustness, a proficiency test should be conducted with other laboratories involved.

Optimization of the gradient composition of the mobile phase was performed after determining the optimum extraction condition. The combination of the mobile phase consisted of 0.1% formic acid in water (v/v) and 0.1% formic acid in MeCN under two different gradient conditions (Table I). The selection of the mobile phase was based on the solubility of the analyte during interaction in the chromatography column and the ionization efficiency in the MS/MS detector. MIT and CMIT are compounds that are easily soluble in water; therefore, the mobile phase that was selected was water with the addition of acetonitrile as an organic modifier. The addition of an organic modifier was needed to retain those compounds in the column and provide a separation process from other compound contents. However, a high organic solvent content can cause ion suppression; therefore, balancing the water and organic phases was particularly important. Moreover, the addition of additive compounds (e.g., formic acid against trifluoroacetic acid) was needed to increase the ionization efficiency.

Ultimately, the Acquity UPLC C18 HSS T3 column was applied because it gave the best result for the peak shape, sensitivity, and retention times when used with 0.1% formic acid in water (mobile phase A) and 0.1% formic acid in MeCN (mobile phase B) (this experiment is not described in this article). In condition 1, MIT had a retention time of 2.46 min as the organic composition increased from the initial moment. In condition 1, the analyte comes out faster than in condition 2 because in the first minute the composition of mobile phase B is greater than that of mobile phase A, and the analyte is more soluble in the organic phase; thus, the analyte is retained less in the stationary phase. Meanwhile, in condition 2, after 2 minutes, the composition is still in the aqueous phase with 100% MeCN; therefore, the analyte is retained in the column for longer, and the retention time can be extended. Condition 2 was chosen for use in the next analysis process because it provides an opportunity for any co-extractants to be removed before the analyte elutes (Figure 2).

In the meantime, optimizing the mass spectrometric conditions was performed by optimizing the tuning conditions and MRM parameters, including the capillary voltage, sample cone, and collision energy. We initially infused the lock mass solution of 100 pg/µL leucine enkephaline, which was used as a reference mass of $[M + H]^+$ with m/z = 556.2766. When the result was deemed acceptable, we proceeded to optimize the MRM parameters by infusing 5 mg/mL solutions of single MIT and MCIT at a flow rate of 0.2 mL/min. Positive Electrospray Ionization (ESI) was chosen as the ionization source for all analytes because both MIT and CMIT are easily positively ionized. For each compound, three fragment ions were selected that may be used for confirmation (the secondary and tertiary fragments) as well as for quantitation (the primary fragment).

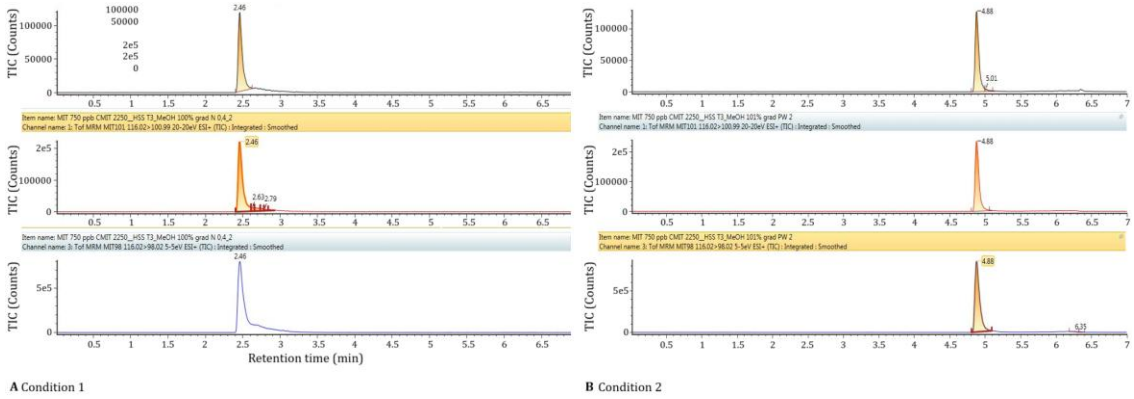

Figure 2. The total ionic chromatogram of methylisothiazolinone (MIT) obtained from two different elution conditions. The retention times of MIT obtained from conditions 1 and 2 were 2.46 and 4.88 min, respectively.

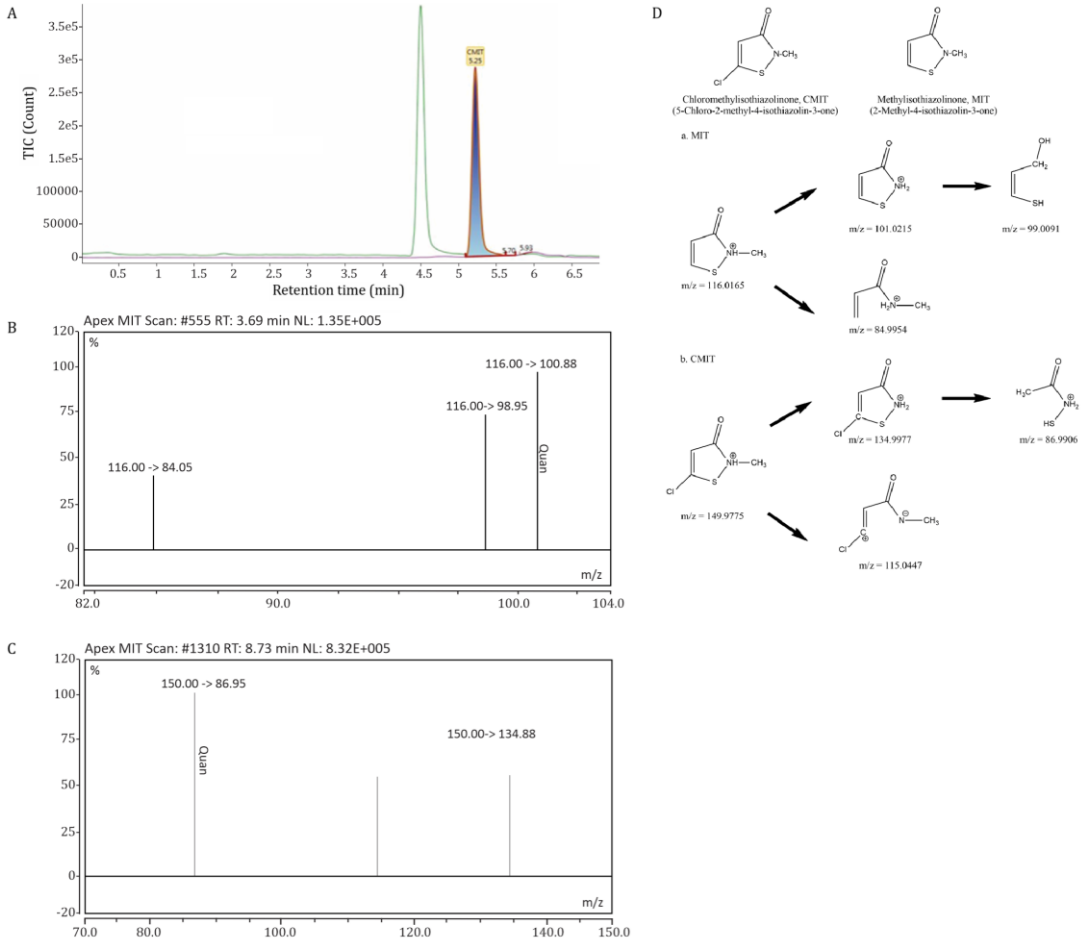

Figure 3. Total ionic chromatogram of methylisothiazolinone (MIT) and chloromethylisothiazolinone (CMIT) obtained by using a gradient elution as in condition 2 (3a), m/z of the molecular ions and fragment ions of MIT (3b) and CMIT (3c) obtained from the proposed methods and proposed fragmentation pathway (3d).

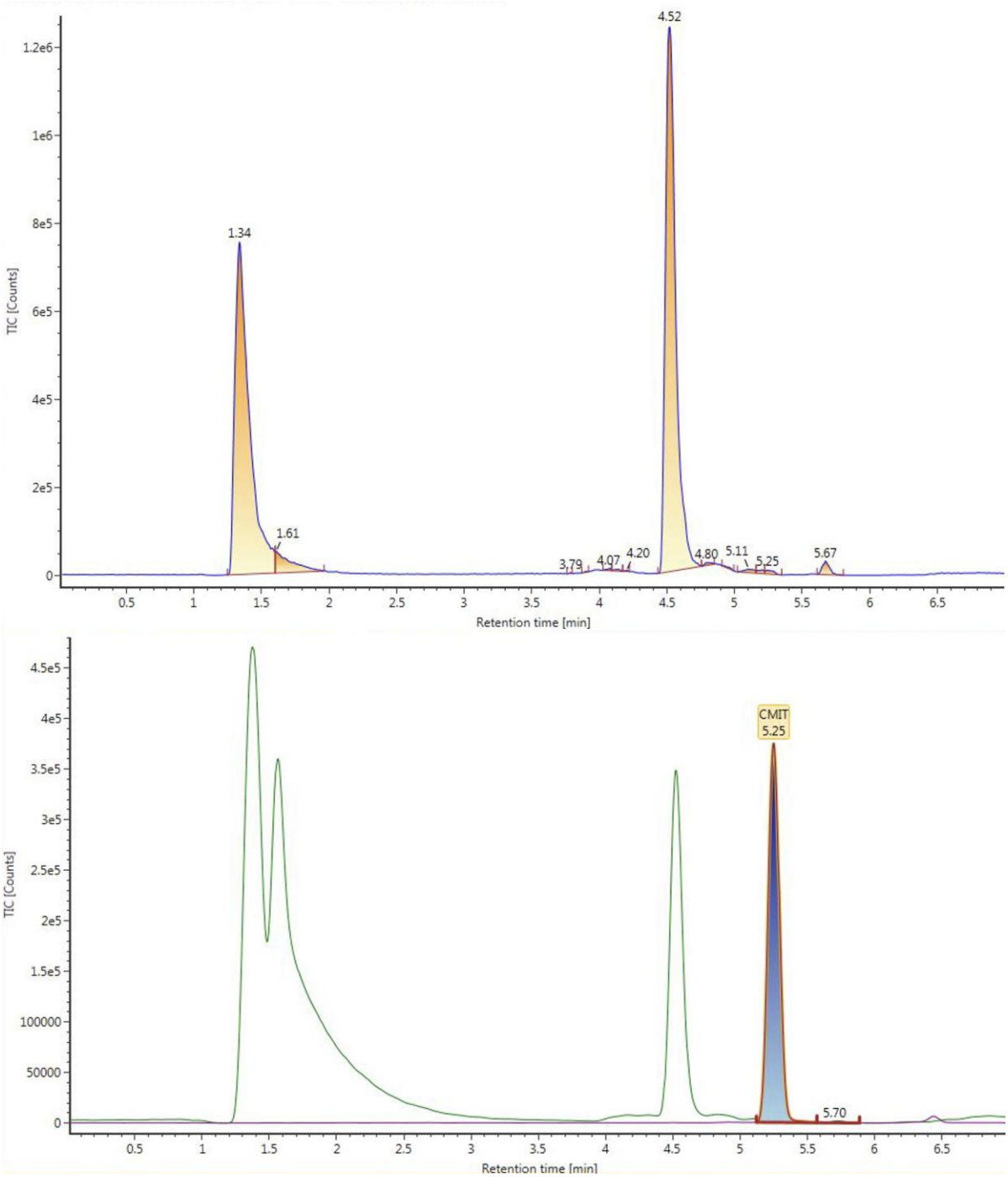

Figure 4. Total ionic chromatogram of the sample containing methylisothiazolinone (MIT) (4a) and a mixture of MIT and chloromethylisothiazolinone (CMIT) (4b).

The $[M + H]^+$ ions were identified as the precursor ions, and the instrument intensity was used to select the product ions. In this study, the Waters Acquity UPLC HSS T3 column was used because it can be operated at a high aqueous mobile phase and is designed to retain polar compounds (Cajka *et al.*, 2022). The MRM was adjusted at m/z 116.0165 to determine the $[M + H]^+$ of MIT, and m/z of 99.0091, 101.0215, and 84.9954 were set to detect the MIT fragment ions (Figure 3b-3c). Meanwhile, for CMIT, m/z 149.9775 was set to detect $[M + H]^+$, and m/z at 134.9977, 86.9906, and 115.0447 were chosen as the signals for the CMIT fragment ions (Figure 3d).

SST

A system suitability test (SST) was performed to confirm the chromatographic system's appropriateness for analytical applications. Six replicate injections of a MIT standard and a mixture of MIT/CMIT standard solutions were analyzed. According to standards from International Council for Harmonisation (ICH) Q2 (R1) (2005) and United States Pharmacopeia (USP) 40 (2021), SST acceptance criteria specify a percent relative standard deviation (%RSD) below 2%. The %RSD values for MIT and CMIT retention times were 0.11% and 0.10%, respectively.

Method validation

Method validation must adhere to the USP 40 and ICH Q2 (R1) guidelines (category IV) to determine the LOD and ensure specificity (ICH, 2005; U.S. Pharmacopeia, 2021). No excipient peak interfered with the analyte peaks, and both MIT and CMIT were completely separated according to the method specifications (Figure 3a). The retention times were 4.52 and 5.25 min for MIT and CMIT, respectively. These showed excellent results compared to the study conducted by Wittenberg *et al.* (2015); the analytes were retained for longer than the second one, which was 1.0 min for MIT and 2.9 min for CMIT.

Moreover, according to the optimization results, three transition ions were obtained compared to the result obtained in the study conducted by Wittenberg et *al.* (2015); therefore, the confidence in the valid test results is greater. The attained correlation coefficients, which were greater than 0.995 for both single MIT and mixture MIT/CMIT, showed that the peak area and concentration have a strong linear relationship.

The summary of the validation parameters determination is provided (Table IIa). The results of this study are lower than those of the study conducted by Ducup de Saint Paul *et al.* (2021), which had a %RSD for the precision determination of MIT and CMIT of 6.8 and 11.5, respectively. Although several validation parameters met the standard criteria and can be applied to analyze the MIT and CMIT content in cosmetic samples, the robustness needs to be evaluated further by conducting proficiency tests with several other laboratories.

Sample analysis

A total of 24 cosmetic products were sampled, including shampoo/conditioners and skin care products, such as lotions and moisturizers. These were categorized as leave-on, leave-in, or rinse-off based on their intended use. Rinse-off samples consisted of shampoo, soap, and feminine hygiene. While leave-on samples included nail polish, lipstick, lotion, face toner, and powder. The chromatography system readily separated the matrix that was co-extracted with the target compound (MIT and CMIT) (Figure 4) The matrix can be eluted between 1.34 and 3.2 min. The test result (Table IIb) showed that three samples were detected as having an MIT concentration in the range of 0.00017–0.0012 μg/g. In the MIT/CMIT mixture, it can be determined that the concentrations of MIT and CMIT were 0.00003–0.00260 and 0.000001–0.000340 μg/g, respectively.

CONCLUSION

An UHPLC-MS/MS has been effectively used to establish a validated method for MIT and CMIT determination in cosmetic products. This method also successfully analyzed single MIT and mixture MIT/CMIT concentrations in 24 commercial samples. MIT and CMIT were adequately separated and the peak had a good shape and notable LOD and LOQ. The linearity, precision, and accuracy were calculated and met the validation requirements. It was found that there were three types of shampoo and one type of soap that contained single MIT or mixed MIT/CMIT. The concentration of single MIT was found in the range of 0.00017–0.0012. μg/g Whereas for the mixed MIT/CMIT, the MIT concentrations were in the range of 0.00003–0.0026 μg/g and 0.000001–0.00034 μg/g for the CMIT concentration.

Table 2a. Validation result of single methylisothiazolinone (MIT) and combination MIT/ chloromethylisothiazolinone (CMIT)

Compound/ng/ml	Calculated Concentration/(ng/ml)	Linearity Range (ng/L)	Linear Regression Equation	Correlation Coefficient and Vx0	Recovery (%)	RSD	LOD (%)
Identification							
Single MIT		-	-	-	-	-	0.000003
Quantification							
Single MIT							
a. 403.12	422.13	375-1125	y = 5233.2x+1201830	r = 1.000	100.26-109.17	1.8	-
b. 806.24	784.59			Vx0 = 1.13	96.52-98.11	1.0	
c. 1209.36	1193.76				97.65-99.77	1.4	
Mixture							
MIT							
a. 107.68	102.19	107.68-323.04	y = 8039.7x+604198	r = 1.000	91.5-98.3	4.0	-
b. 215.36	218.81			Vx0 = 1.2	100.2-103.0	1.4	
c. 323.04	323.04				99.2-99.9	0.3	
MCIT							
a. 295.36	277.05	295.36-886.08	y = 3340.5x+206085	r = 0.996	86.5-101.1	7.0	-
b. 590.72	606.37			Vx0 = 3.5	102.2-103.1	0.4	
c. 886.08	867.92				97.1-98.8	0.8	

Table 2b. Concentration of methylisothiazolinone (MIT) and chloromethylisothiazolinone (CMIT) in the various commercial product samples

Category	Number of Sample	Number of positive sample	Concentration of single MIT (µg/g)	Concenntration of MIT and MCIT in mixture (µg/g)
Shampoo	9	3	0.00017-0.0012	MIT 0.00003-0.0026 CMIT 0.000001-0.00034
Soap	5	1		
Feminine Hygiene	1	-		
Nail Polish	1	-		
Lipstick	1	-		
Lotion	1	-		
Face Toner	1	-		
Powder	2	-		

The analytical technique presented here can be used to evaluate a wide range of MIT and CMIT preservatives used in cosmetic products that can be applied throughout Indonesia and even in remote areas. This technique could be used to monitor how often MIT and CMIT are mislabeled on cosmetic product ingredient lists. Inaccurate or missing ingredient labels can be problematic for consumers and healthcare providers who are trying to avoid items containing these potential skin allergens.

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CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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