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Screening and detection of methylisothiazolinone and chloromethylisothiazolinone in cosmetics by UPLC-MS/MS

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Abstract: Methylisothiazolinone (MIT) and chloromethylisothiazolinone (CMIT) cause allergic contact dermatitis and are banned cosmetics ingredients, except in rinse-off products. However, their presence has been detected in cosmetics. We report a UPLC–tandem MS/MS screening method for their simultaneous determination in cosmetics. To facilitate extraction from various matrices, pretreatment methods were developed for each sample type. The method was optimized through a series of assessments, including specificity, LOD, LOQ, linearity, recovery, stability, precision, and accuracy. The LODs and LOQs for MIT ranged from 0.054 and 0.163 μg mL^{-1} whereas those for CMIT ranged from 0.040 and 0.119 μg mL^{-1}. The linear correlation coefficients (r^2) were higher than 0.999. Relative standard deviations (RSDs) for both intra- and inter-day measurements ranged from 0.3 ~ 13.6 %. Recoveries at three different concentrations were within 87.9 ~ 118.9 %. The RSD for stability measurements of spiked samples was within 7 %. These results confirm the suitability of the developed method for the simultaneous quantitation of MIT and CMIT in cosmetics. Samples of 320 color cosmetics, including eyeshadows, solid lipsticks, liquid lipsticks, and nail polishes were analyzed using the developed method, and two of them were found to contain both MIT and CMIT and one of them was found to contain only MIT. This data and the method will aid the regulation of ingredients used in cosmetics.

Key words: LC-MS/MS, methylisothiazolinone, chloromethylisothiazolinone, cosmetics, screening

1. Introduction

The globalization of beauty-related products and the ever-growing interest of their use is contributing to the growth of the cosmetics market all over the world. The domestic Korean cosmetics market is gradually expanding due to the diversification of consumer age and the export and import of cosmetics.[1,2] In addition to this trend, the presence of harmful substances in cosmetics is also increasing.[3] MIT and CMIT are heterocyclic organic compounds which are used for preventing bacterial and mildew growth in various types of consumer products, such as cosmetics, hair and skin-care products, cleaning

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agents, and fabric softeners.[4-7] The sensitization of skin to biocidal chemicals has become widely prevalent, and these chemicals can also penetrate the skin and react with skin proteins, which causes contact dermatitis.[8-10] Until the reports and recognition of allergic contact dermatitis, a mixture of CMIT and MIT in a 3:1 ratio has been widely used in various types of consumer products.

In 1990, Europe lowered the maximum authorized concentration of CMIT in rinse-off cosmetic products from 30 μg/mL to 15 μg/mL. The corresponding non-halogenated derivative MIT was approved in 2005 and was less effective than CMIT as a biocide. Therefore, it was permissible up to 100 μg/mL as a preservative in leave-on (hand and body lotions and moisturizers and sun tanning lotions) and rinse-off cosmetics (shampoos, surfactants, and conditioners). However, in 2017, the European Union banned the distribution of leave-on cosmetics containing MIT and lowered its maximum allowable level to less than 15 μg/mL in rinse-off cosmetics (Annex V, entry 57, of Regulation (EC) No 1223/2009). According to China's Hygienic Standard for Cosmetics 2007, the level of MIT in cosmetics is limited to 0.01 %. The mixture of CMIT and MIT is permissible in rinse-off products in a 3:1 ratio with a combined limit level of 0.0015 %, and further increase of the MIT level in the composition is not permissible for cosmetics. According to the 'on Safety Standards etc. of Cosmetics' regulation of the Korean Ministry of Food and Drug Safety (MFDS), up to 0.01 % of MIT is permissible in rinse-off cosmetics, and the mixture of CMIT and MIT must be below 0.0015 % at a 3:1 ratio. Although the use of CMIT and MIT above these limits is prohibited in commercial products, they are illegally added by some manufacturers to improve preservative efficacy. Further, since the regulation of MIT and CMIT concentrations in cosmetics differs from country to country, there are many cases where products that should not be distributed in Korea are sold to overseas purchase. Therefore safety management for this must be strengthened (*Table* 1).

Table 1. MIT and CMIT regulations by country

Compounds	Europe	China	Korea
MIT	15 μg/mL (rinse-off)	100 μg/mL (leave-on, rinse-off)	100 μg/mL (rinse-off)
Mixture (CMIT:MIT = 3:1)		15 μg/mL (rinse-off)	

With the widespread use of MIT and CMIT in various types of consumer products and the corresponding growth in the potential exposure risks to consumers, the interest and controversy concerning their stability and adverse effects are increasing. Therefore, safety management and supervised scientific monitoring of illegal cosmetics need to be strengthened to ensure health and safety. Isothiazolinones have been analyzed using GC-MS and LC-MS/MS. Although GC-MS delivers good performance in terms of separation efficiency and identification capabilities, the need for derivatization of different classes of biocides has limited its applications.[11,12] On the other hand, LC-MS/MS can reduce the analysis time for the determination of biocides and does not require derivatization. Furthermore, due to its rapid analysis, ease of operation, and the highest sensitivity, LC-MS/MS has been used for the identification and quantification of MIT and CMIT in cosmetics.[13-14] Despite the availability of methods as they use simple extraction with methanol alone for the analysis of MIT and CMIT in paints, food packaging paper, and cosmetics such as hair conditioners, lotions, and gels, several limitations exist in the analysis of biocides in color cosmetics comprising various matrices.[15-17] Due to the structural complexities of cosmetic ingredients, the determination of pretreatment methods is essential for accurate analysis of various types of cosmetics. The purpose of this study is to monitor the presence of MIT and CMIT in 320 color cosmetics marketed in Korea, and development of methods for their efficient and reliable quantification in eye shadows, solid and liquid lipsticks, and nail polishes by focused development of preprocessing methods.

2. Experimental

2.1. Chemicals and reagents

MIT was purchased from Sigma-Aldrich (St. Louis, MO, USA). CMIT and CMIT-d_3 were obtained from TRC (Toronto, Ontario, Canada). The chemical structures of these three compounds are shown in *Fig.* 1. The stock solutions were prepared by dissolving each compound (10 mg) in methanol (10 mL), and the standards were stored in a refrigerator (at 4 °C) until use. CMIT-d_3 was used as the internal standard (IS). Chloroform was obtained from Biopure (Waterlooville, UK). Methanol and acetonitrile of HPLC-grade were purchased from Burdick and Jackson (Muskegon, MI, USA), and formic acid was purchased from Sigma-Aldrich (St. Louis, MO, USA). High-purity deionized water was obtained from a Milli-Q purification system (Millipore, Bedford, MA, USA) at 18.1 MΩ. All solvents were filtered using 0.2 μm polyvinylidene difluoride (PVDF) filters. A total of 320 samples, including those of eye shadows, solid and liquid lipsticks, and nail polishes, were purchased from online and offline markets.

2.2. Instrumental conditions

The UPLC-MS/MS experiments were carried out using an Acquity UPLC™ system equipped with Xevo TQ mass spectrometer (Waters, Milford, CT, USA). For the separation, a Waters Acquity UPLC HSS T3 column (2.1 mm × 100 mm, 1.7 mm) was used, and the column oven temperature was maintained at 30 °C. The mobile phase (solvent A: 0.1 % formic acid in distilled water; solvent B: 0.1 % formic acid in acetonitrile) flow rate was 0.2 mL/min, and the injection volume was 1 μL. The gradient parameters were as follows: Initial-2 min, 0 % B; 2-7 min, 0 % B to 100 % B; 7-9 min, 100 % B; 9-9.1 min, 100 % B to 0 % B; 9.1-11 min, 0 % B into the ion source using a valve switch to prevent contamination. The MS was operated in the positive ESI mode. The desolvation gas flow and temperature of the positive ion mode were 600 L/h (N_2) and 500 °C, respectively. A capillary voltage of 2.7 kV and a collision gas flow rate of 50 L/h was used to achieve optimal analytical conditions. Other parameters were optimized for each transition (*Table* 2).

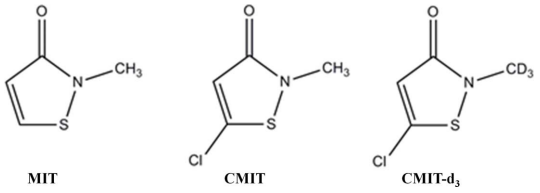

Fig. 1. Chemical structures of MIT and CMIT and CMIT-d_3

2.3. Sample preparation

2.3.1. Eyeshadows and liquid lipsticks

Each sample (approximately 0.2 g) was extracted with methanol (4 mL) by vortexing for 1 min. IS in methanol (1 mL, 10 μg/mL) was added to the solution of each sample. Further extraction was performed by ultrasonication for 30 min, followed by addition of methanol to make up the final volume to 10 mL. The extracts were centrifuged for 10 min at 3000 rpm, and the upper layer of the extract was filtered through a 0.2 μm PVDF filter (Millipore, Milford, USA) prior to LC-MS/MS analysis.

Table 2. LC-MS/MS MRM transition parameters for the MIT and CMIT

MRM No.	Compounds	Precursor ion (*m/z*)	Product ion (*m/z*)	CV (V)	CE (eV)
1	MIT	116.10	70.95	30	15
			99.00		15
			101.00		20
2	CMIT	150.10	87.00	30	30
			96.00		20
			115.00		20
			119.00		20

2.3.2. Solid lipsticks

The sample (0.2 g) was extracted with chloroform (1 mL) by vortexing for 1 min, and methanol (3 mL) was added to the solution, followed by the addition of 1 mL of IS in methanol (10 μg/mL). Further extraction was performed by ultrasonication for 30 min to ensure complete dissolution, followed by the addition of methanol to make up the final volume to 10 mL. The extract was centrifuged for 10 min at 30000 rpm, and the upper layer was filtered through a 0.2 μm PVDF filter prior to UPLC–MS/MS analysis.

2.3.3. Nail polish

The sample (0.4 g) was extracted with methanol (4 mL) by vortexing for 1 min, and 2 mL I.S in methanol (10 μg/mL) was added. The mixture was sonicated for 30 min. After making up the volume to 10 mL with methanol, the extract was centrifuged for 10 min at 30000 rpm. The supernatant of the extract (5 mL) was placed in a centrifuge tube, and 5 mL of 50 % acetonitrile in 1 % formic acid was added. The immediate generation of liquid crystals was observed by the reaction of cellulose and the acid, and the mixture was centrifuged for 10 min at 30000 rpm. The resulting upper layer was filtered through a 0.2 μm PVDF filter prior to LC-MS/MS analysis.

2.4. Method validation

The purpose of validation of an analytical procedure is to demonstrate its suitability for the intended purpose. The analytical method for MIT and MCIT was validated for specificity, LOD, LOQ, linearity, precision, accuracy, recovery, and stability according to the requirements by the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use. Each type of cosmetics (eye shadows, solid and liquid lipsticks, and nail polishes), which did not contain the target compound, were used as matrix-blank samples. Specific identification of each compound was carried out by injecting a blank sample spiked with a standard solution of MIT and CMIT.

3. Results and Discussion

3.1. Sample preparation

Cosmetic matrices are diverse and complex, largely due to the variations in their formulation. Taking these variations into account, we employed efficient extraction procedures for cosmetics which were formulated differently.

3.1.1. Eyeshadows and liquid lipsticks

For eyeshadows and liquid lipsticks, methanol was chosen for extraction. Methanol solutions have been proven to be fast and effective for extracting preservatives from matrices. The eye shadows and liquid lipsticks were suspended in methanol and were dispersed completely.[18]

3.1.2. Solid lipsticks

Solid lipsticks are classified as wax-based cosmetics that mainly contain fats or oily materials. These materials must be dissolved fully before the LC-MS/MS injection and were hence pretreated with chloroform, which was found to be an effective extraction solvent.[18]

3.1.3. Nail polish

Nitrocellulose is used in nail polish formulations, and the nitrocellulose crystal lattice swells extensively due to the formation of intermolecular hydrogen bonds when formic acid molecules penetrate the crystal lattice. Eventually, the rigid framework of the crystal lattice is lost, which leads to hydrolysis in both crystalline and amorphous zones. A small amount of formic acid was used in the mobile phase to aid ionization in UPLC-MS/MS analysis. To prevent the formation of liquid crystals by the reaction of nitrocellulose with the acid, the matrix was removed by the addition of formic acid during the nail polish pretreatment. Some amount of the matrix was removed during all processing steps using centrifugation (30000 rpm).[18-20]

3.2. Method validation

As shown in *Fig.* 2, The results of specificity

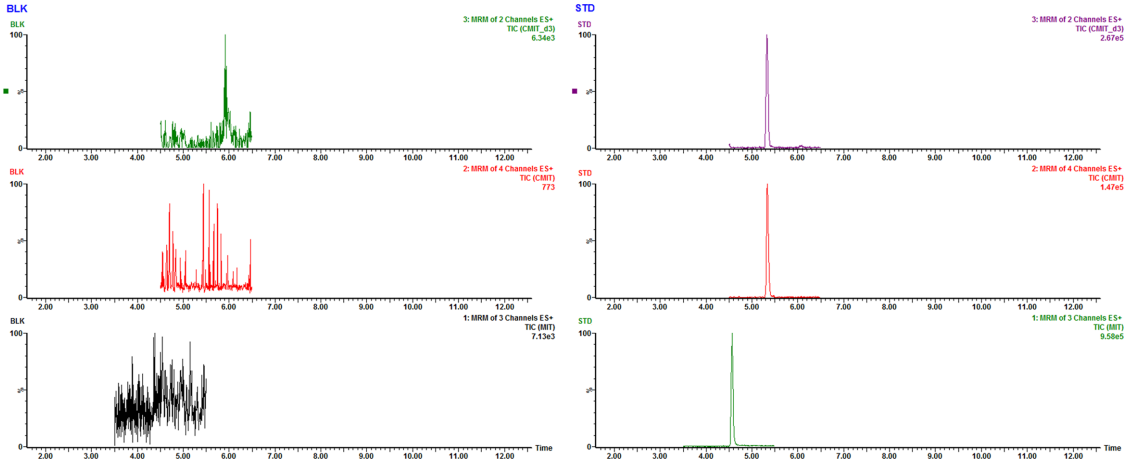

Fig. 2. Ion chromatograms of matrix-blank and standards by LC-MS

analysis showed that no interference peaks were detected in the blank matrix samples. The LOD and LOQ were calculated using real samples spiked with standard solutions. The LOD was defined with a signal-to-noise ratio (S/N) of 3, and the LOQ was defined with an S/N of 10. Notably, the LODs of the samples were in the 0.040 ~ 0.054 μg mL^{-1} range, while the LOQs were in the 0.119 ~ 0.163 μg mL^{-1} range (*Table* 3).

The linearity was evaluated for each matrix-blank sample at six different concentrations, which ranged between 0.12 and 3.26 μg mL^{-1}. The results indicated excellent correlation between the peak area ratios (STD area/IS area) of the compounds in the ranges tested (R^2 > 0.99). The results of LOD, LOQ, and linearity of various sample types are summarized in *Table* 4. Recovery was obtained at three concentration levels (0.16, 1.16, and 3.26 μg/mL) and in four different blank sample matrices (eye shadow, solid lipstick, liquid lipstick, and nail polish) and was

Table 3. Determined limit of detection (LOD) and limit of quantitation (LOQ) for the MIT and MIT compounds for cosmetic products

Compound	LOD (μg/mL)				LOQ (μg/mL)			
	Eyeshadow	Liquid lipstick	Solid lipstick	Nail polish	Eyesh adow	Liquid lipstick	Solid lipstick	Nail polish
MIT	0.054	0.054	0.054	0.054	0.163	0.163	0.163	0.163
CMIT	0.040	0.040	0.040	0.040	0.119	0.119	0.119	0.119

Table 4. The linearity of five concentration of MIT and CMIT compounds

Type	Compound	Calibration curve	Linear range	R^2
Eyeshadow	MIT	y = 2.4404x – 0.021	0.16-3.26	0.9998
	CMIT	y = 0.371x – 0.0259	0.12-2.38	0.9987
Lipstick (liquid)	MIT	y = 2.5372x – 0.0049	0.16-3.26	0.9989
	CMIT	y = 0.3855x – 0.0219	0.12-2.38	0.9987
Lipstick (solid)	MIT	y = 2.6065x – 0.1114	0.16-3.26	0.9994
	CMIT	y = 0.3218x – 0.0158	0.12-2.38	0.9986
Nail polish	MIT	y = 2.2995x – 0.0503	0.16-3.26	0.9997
	CMIT	y = 0.3167x – 0.0127	0.12-2.38	0.9995

Table 5. The recovery of cosmetic compounds for different concentrations

Compounds		Conc. (μg/mL)	Recovery (%)	Precision (RSD%)
Eyeshadow	MIT	0.16	108.1	6.7
		1.16	109.0	2.4
		3.26	108.3	1.4
	CMIT	0.16	96.7	3.4
		1.16	104.3	0.7
		3.26	103.4	2.3
Lipstick (liquid)	MIT	0.16	99.8	4.5
		1.16	104.7	1.8
		3.26	102.6	3.1
	CMIT	0.16	115.3	1.4
		1.16	101.7	2.1
		3.26	101.5	4.1
Lipstick (solid)	MIT	0.16	106.9	4.6
		1.16	118.9	2.2
		3.26	115.4	5.7
	CMIT	0.16	109.2	6.5
		1.16	102.1	2.5
		3.26	102.4	3.7
Nail polish	MIT	0.16	87.9	3.9
		1.16	97.2	1.8
		3.26	94.7	1.4
	CMIT	0.16	103.6	4.4
		1.16	105.8	0.4
		3.26	98.9	2.3

calculated as a percentage. Recoveries were studied in triplicate and ranged from 99 ~ 111 % for MIT and 93 ~ 104 % for CMIT. These results indicated acceptable recovery, and therefore, the proposed method is suitable for application to complex matrices (*Table* 5).

For determining the accuracy and precision of the method, intra-day, and inter-day analyses were performed with matrix blank samples spiked with three different concentrations, and the results are summarized in *Table* 6. Precision was expressed as the RSD value of the results obtained at the three different concentrations. Accuracy ranged from 80.24 to 119.90, with the RSD ≤ 14.19 % for RSD of ≤ 12.82 % for inter-day measurement. The stock solution stability was investigated over 48 h at room temperature, and the RSD of the measurement was ≤ 14.25 % (*Table* 7).

3.3. Application to real samples

The developed LC-MS/MS method was employed for the quantitative determination of MIT and CMIT in four different cosmetic products (eye shadow, solid lipstick, liquid lipstick, and nail polish). LC-MS/MS peaks corresponding to MIT, CMIT, and CMIT-d_3 (IS) were observed at the retention times of 4.68, 5.43, and 5.43 min, respectively. Mass fragmen-

Table 6. The precision and accuracy of three concentration of MIT and CMIT compounds

Compounds		Conc. (μg/mL)	Intra-day		Inter-day	
			Accuracy (%)	Precision (RSD%)	Accuracy (%)	Precision (RSD%)
Eyeshadow	MIT	0.16	105.7	2.1	102.9	7.7
		1.16	94.9	2.3	87.6	7.6
		3.26	95.0	3.2	88.1	7.5
	CMIT	0.12	115.8	6.7	121.4	4.0
		1.63	101.1	2.8	88.7	8.8
		2.38	108.1	2.7	93.6	10.1
Lipstick (liquid)	MIT	0.16	95.4	4.7	104.9	13.6
		1.16	81.9	2.1	87.7	13.3
		3.26	82.0	2.0	86.7	9.3
	CMIT	0.12	120.3	1.0	119.8	5.9
		1.63	89.9	1.0	84.6	5.6
		2.38	99.8	3.7	88.2	11.4

Table 6. Continued

Compounds		Conc. (μg/mL)	Intra-day		Inter-day	
			Accuracy (%)	Precision (RSD%)	Accuracy (%)	Precision (RSD%)
Lipstick (solid)	MIT	0.16	102.0	1.1	99.8	2.9
		1.16	102.3	1.5	100.1	3.3
		3.26	98.8	1.1	100.0	1.1
	CMIT	0.12	103.1	5.4	93.2	10.6
		1.63	98.3	2.0	98.1	0.9
		2.38	102.0	1.2	101.6	0.3
Nail polish	MIT	0.16	101.8	3.1	102.9	4.8
		1.16	99.5	1.9	94.3	4.8
		3.26	95.0	0.8	93.6	2.1
	CMIT	0.12	112.0	5.5	112.3	4.5
		1.63	98.8	1.6	97.9	4.5
		2.38	97.4	0.8	97.4	3.0

Table 7. The stability of the current LC-MS/MS method for the analysis of MIT and CMIT solutions stored for 24 or 48 hour

Compounds	Conc. (μg/mL)	24 h	48 h
		RSD%	
MIT	0.16	7.0	4.0
	1.16	4.0	5.1
	3.26	2.8	3.6
CMIT	0.12	5.1	6.8
	1.63	3.6	2.3
	2.38	1.9	4.0

tation patterns for the samples containing these biocidal chemicals matched well with standard mass spectra. In the analysis of the 320 cosmetic sample, both MIT and CMIT were detected in two samples and MIT alone was detected in one sample. Among those three samples, the detected concentrations of MIT ranged from 11.45 to 34.63 μg/g and that of CMIT ranged from 17.19 to 35.24 μg/g (*Table* 8).

Isothiazolinone can cause allergic contact dermatitis. Since the regulations for its concentration differ from country to country, the presence of MIT and CMIT at levels higher than the allowed limits in color-cosmetics is a possibility, due to which, regular and consistent monitoring of their presence in cosmetic products is required. The developed method described here has been validated and may be applied for detecting the presence of MIT and CMIT in a wide variety of cosmetics (*Fig.* 3).

4. Conclusions

A reproducible and sensitive UPLC-MS/MS method

Table 8. The number of MIT and CMIT detections in cosmetic samples

		Eyeshadow	Lipstick		Nail polish	Total
			Liquid	Solid		
The number of samples		51	104	33	132	320
The number of detection (Detection amount (μg/g))	MIT	n.d.*	n.d.*	n.d.*	3 (11.45 ~ 34.63)	3
	CMIT	n.d.*	n.d.*	n.d.*	2 (17.19 ~ 35.24)	3

*Not detected

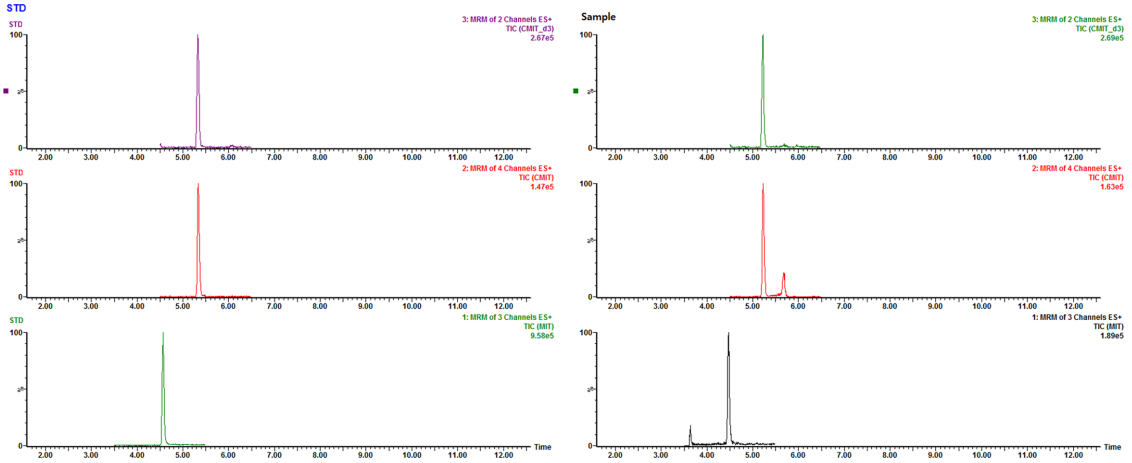

Fig. 3. Ion chromatograms of standards and a real sample by LC-Ms

was developed for the determination and quantification of MIT and CMIT in color cosmetics. Color cosmetics have diverse matrices, to account for which, we have established pre-treatment methods for each eyeshadow, solid lipstick, liquid lipstick, and nail polish. The established method was validated using various parameters and was found to be specific, precise, accurate, linear, and stable. A total of 320 samples, including 51 eye shadows, 137 lipsticks, and 132 nail polishes obtained from online and offline markets were screened to evaluate the practicality of this method. CMIT and/or MIT were detected in three samples among them. This study demonstrates the successful application of the method for the detection of MIT and CMIT in three types of cosmetic products. This method may be used to ensure reliable and steady monitoring of adulterated cosmetics, and may thereby find prominent use in public health protection.

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