Analytical Method Development for Determining Formaldehyde in Cream Cosmetics Using Hyphenated Gas Chromatography

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ABSTRACT: Formaldehyde has been reported to be a potential human carcinogen due to its toxicity. However, formaldehyde releaser substances are still widely used as a preservative in cosmetics. Researchers have developed various methods for determining formaldehyde. One of the problems involved in the standard method is that of obtaining a derivatization agent, especially for routine analysis in the National Agency of Drug and Food, Indonesia. Therefore, this study aimed to develop a new method using gas chromatography-mass spectrometry (GC-MS) and gas chromatography-flame ionization detection (GC-FID). The significant modifications involved optimizations of five series of concentrations of p-toluenesulfonic (PTS) acid in ethanol (acidified ethanol), used as the derivatization agent, and the conditions of time and temperature of the reaction to yield the highest peak area. In addition, sample analysis was also carried out using the 2,4-dinitrophenylhydrazine (DNPH) method with high-performance liquid chromatography (HPLC) to compare the quantification results. The validated method showed intraday and interday precision, an accuracy (% RSD) of less than 3.7%, confidence interval 95.0−105.0%, a limit of detection and quantitation of 0.0099 and 0.0329 μg/mL (for DNPH by HPLC-DAD), 0.0158 and 0.0528 μg/mL (for PTS by SHS-GC-MS), and 1.1287 and 3.7625 μg/mL (for PTS liquid by GC-FID), respectively. These results have met the requirements for a validated analytical method and could be applied for routine analysis.

INTRODUCTION

Formaldehyde releasers such as diazolidinyl urea (DU) and imidazolidinyl urea (IU) are the most widely used preservatives in cosmetics.1 However, despite these components being commonly used in cleansing and skincare cosmetics products, they also might potentially cause allergies (allergens) when used in excess.2 According to the International Agency for Research on Cancer (IARC) in 2006, formaldehyde was classified into group I as a human carcinogen based on evidence that formaldehyde substance can cause nasopharyngeal cancer and myeloid leukemia.3 Therefore, to meet the safety, efficacy, and quality requirements for cosmetics, notably formaldehyde releasers, it is crucial to analyze these products using the latest, sensitive, and validated analytical method. This method should have the characteristics for identifying and quantitatively determining the levels of formaldehyde released from the preservatives used in cream cosmetics.

Several analysis methods of formaldehyde have been developed between 2015 and 2019, including the DLLME-LC UV–vis method,4 high-performance liquid chromatography-diode array detector (HPLC-DAD) derivatization of 2,4-dinitrophenylhydrazine (DNPH),5 and GC-MS derivatization of DNPH.6 However, further modification is needed to update technology advancement and regulation. Gas chromatography-mass spectrometry (GC-MS) and flame ionization detection (GC-FID) determine the levels of formaldehyde released from the formaldehyde releaser class of preservatives in cream cosmetic products.

Derivatization using 2,4-dinitrophenylhydrazine (DNPH) is the most commonly used method for formaldehyde determination. However, this DNPH reagent is currently difficult to obtain due to the Indonesia Government Regulations since 2018. Therefore, modification of the process is urgently needed. An alternative derivatization using paratoluenesulfonic acid is proposed to obtain volatile diethoxymethane as a product of the reaction of formaldehyde and ethanol as solvent with an acid catalyst. Its several advantages can be applied in the laboratories of Indonesia, such as the validated method, efficiency in time, and, most importantly, the availability of the reagent compared to DNPH.

The purpose of this study is to modify the analysis method by the instrument of gas chromatography-mass spectrometry.
Formaldehyde can be determined by gas chromatography after derivatization with p-toluenesulfonic acid in ethanol to form diethoxymethane with a molecular mass of 104.15 g/mol. A previous study has developed and validated the analysis method of formaldehyde contamination in medicinal excipient samples using this technique and the GC-MS instrument. Bashir Daoud Agha Dit Daoudy et al. further developed this method to analyze formaldehyde in medicinal excipients using GC-FID. This derivatization may modify the functional groups of the compound, improve its stability, and enable its detection. The scheme of the derivatization reaction between formaldehyde and ethanol with p-toluenesulfonic acid is shown in Figure 1.

In this development of the formaldehyde analysis method, the use of the internal standard acetone can improve recovery and precision due to the analyte loss during the testing process. The internal standard requires similar physical and chemical properties to the analyte, high purity, not being present in the sample matrix, and being well separated from the analyte or other components contained in the matrix.

p-Toluenesulfonic acid in ethanol was chosen as the solvent and derivatizing agent. Formaldehyde can react quickly with ethanol containing an acid catalyst to produce volatile acetal dimethoxymethane with a boiling point of 88 °C so that its level can be determined by gas chromatography. Ethanol is also able to disperse the cosmetic cream matrix perfectly. The amount of ethanol used must be in excess so that the derivatization reaction can take place completely. p-Toluenesulfonic acid is a novel catalyst in organic chemistry. It is a commercial sulfonic acid catalyst with a pK_a-value of −2.8. This catalyst has several benefits, including low cost, not being in an oxidizing solid state, and being easy to handle. It is regularly used as the simplest and more usable catalyst in chemical reactions.

Method modification was started with the optimization involving the column selection, determination of temperature and incubation time, determination of the optimum concentration of p-toluenesulfonic acid in the ethanol used, and the temperature program that can provide system suitability test results meeting the relative standard deviation (RSD) acceptance criteria of retention time and area, resolution, the tailing factor, and the theoretical plate value or column efficiency.

The column used for optimization was column 1 MS, 5MS, and Wax 30 m (0.25 mm × 0.25 μm). The more nonpolar 1 and 5 MS column gave a peak response with a tailing factor (T_f) of more than 2.5 because there were peaks of interference compounds that cannot be separated and thus disrupted the analysis. T_f ranging from 0.9 to 1.4 is considered as good. By using a more polar 30 m Rtx-Wax column, the peaks of the interference compounds could be separated with a resolution (R) of more than 1.5 and a T_f of 0.985. The formaldehyde derivative diethoxymethane has a low boiling point and resulted in a swift retention time of 2.9 min, not being held back by the column; hence, a wax column with a larger film thickness was chosen to increase its capacity factor according to the general requirements of chromatography, 1 ≤ k’ ≤ 10. The wax column used at the beginning of the optimization had a film thickness of 0.25 μm, resulting in a capacity factor of 0.7. For further testing, a wax column with a film thickness of 0.5 μm was used with a capacity factor of 1.54. A larger film thickness of the column is most suitable for analytes with low boiling points (such as organic compounds and volatile gases), so that the analyte will be retained longer.

Optimization of temperature and incubation time was carried out to determine the optimum condition that results in the best area response so that precision and accuracy values that meet the requirements can be obtained. Optimization was carried out at five concentrations of p-toluenesulfonic acid in ethanol, and the optimization results showed that the highest increase in peak response occurred at a concentration of 1.0%.

Optimization of the temperature program aims to produce system suitability test data that meets the requirements,
including $T_f$, $R$, and column efficiency or theoretical plate value ($N$). At a constant temperature elution during the analysis process, the peak response was obtained with a large tailing factor because it was unable to separate the peaks of several components. Therefore, this analysis used the temperature programmed to start at 34 °C and hold for 15 min, increasing by 40 °C per minute until it reaches 220 °C and then hold for 5 min. The optimization results of $p$-toluenesulfonic acid derivatization are shown in Figure 2.

Method validation was started with the selectivity test to ensure the analyte is not affected by the presence of other components by comparing the solvent, blank, standard, and spiked sample and another compound with similar physical and chemical properties as the impurity or degradation product that may be contained in the cream cosmetic products.\textsuperscript{18,19} The chromatogram selectivity test results for the formaldehyde derivative and other structurally similar compounds are shown in Figure 3.

Correlation coefficient ($r$) and coefficient variance regression ($V_{x0}$) were used to approve the linearity test.\textsuperscript{20,21} The linearity of the DNPH-HPLC-DAD method was obtained with an $r$ of 0.9999, $V_{x0}$ of 0.61%, and a concentration range of 0.5–4.0 μg/mL. The linearity of the derivatization method using 1% $p$-toluenesulfonic acid in ethanol static headspace GC-MS was obtained with $r = 1.0000$ and $V_{x0} = 1.62\%$ and concentration ranging from 2.0 to 20.0 μg/mL (Figure 4). The linearity of the derivatization method using 1.0% $p$-toluenesulfonic acid in ethanol GC-FID with liquid injection techniques was obtained with $r = 0.9999$ and $V_{x0} = 1.35\%$ and concentration ranging from 100.0 to 800.0 μg/mL.

The LOD and LOQ of the three methods were calculated from the linearity test and obtained as follows: 0.0099 and 0.0329 μg/mL for HPLC-DAD; 0.0158 and 0.0528 μg/mL for GC-MS; and 1.1287 and 3.7625 μg/mL for GC-FID.

The accuracy test was done by spiking the formaldehyde standard solution with a known concentration to the sample matrix, and comparing the results obtained from the test with the standard concentration obtained theoretically. The accuracy is expressed as the recovery value,\textsuperscript{8} and the results are shown in Tables 1a and 1b.

The precision test was performed intraday for repeatability and interday for intermediate precision. The interday precision was carried out in six repetitions on three different days. The precision parameters measured were RSD, confidence interval (CI),\textsuperscript{9} Horrat value, and relative intensity (% base peak) of the spiked sample solution compared to the standard solution for the GC-MS method. Diethoxymethane has three m/z confirmation ions, namely 31.0, 59.0 as the base peak, and 103.0. The result of the precision test is shown in Table 2. The relative intensity (%) of mass (m/z) by GC-MS can be seen in Table 3, and the mass spectrum for diethoxymethane as the derivatization product from standard solution, sample solution, spiked sample solution, and diethoxymethane from the library are shown in Figure 5.
Table 1a. Results of the Accuracy Test with Three Different Concentrations of HPLC-DAD and the GC-FID Method\(\textsuperscript{a}\) (Revised)

| concentration (µg/mL) | DNPH method HPLC-DAD | p-toluenesulfonic acid liquid GC-FID |
|-----------------------|-----------------------|-------------------------------------|
| %recovery             | RSD (%)               | %recovery                           | RSD (%)               |
| 1                     | 101.16                | 0.22                                | 101.50                | 1.48                      |
| 2                     | 101.15                | 0.50                                | 101.37                | 0.56                      |
| 3                     | 100.82                | 0.59                                | 101.99                | 1.02                      |

\(\textsuperscript{a}\)Acceptance criteria: %Recovery: 95–105%; RSD: 3.7% DNPH (2,4-dinitrophenylhydrazine). HPLC-DAD (high-performance liquid chromatography-diode array detector). SHS-GC-MS (static headspace-gas chromatography-mass spectrometry). GC-FID (gas chromatography-flame ionization detection). RSD (relative standard deviation).

The samples were analyzed when the validation method met all requirements. The samples tested were six samples obtained from post-market surveillance sampling for skincare cosmetics at the National Agency of Drug and Food Control Provincial Office in Bandung, Indonesia. The level of formaldehyde released in the cream products was analyzed using GC-MS, GC-FID, and HPLC-DAD methods, and the level of preservatives was analyzed using the HPLC-DAD method with a gradient elution system. The preservatives level in cream cosmetics is related to the level of formaldehyde released. The assay results of the six cream samples shown in Table 4 have met all requirements.\(\textsuperscript{22}\)

Based on these results, the proposed GC-MS method can be accepted as an analytical method for routine analysis. Moreover, the results obtained from the GC-MS method were statistically similar to those obtained from the DNPH derivatization method using HPLC, which is the most stable method. Formaldehyde analysis using GC-MS has some advantages: it needs a shorter time for the preparation and involves a more economical derivatizing agent compared to DNPH compounds, as shown in Table 5.

## MATERIALS AND METHODS

### Preparation of the Solvent and Solutions

The solvent was prepared by dissolving 10.0 g of p-toluenesulfonic acid monohydrate in 1000 mL of ethanol (1.0%). Standard solutions of formaldehyde, formic acid, diethoxymethane, n-hexane, cyclohexane, and acetone were dissolved in 5 mL of the solvent prepared in volumetric flasks to obtain a concentration of 1 µL/mL for each standard solution. The internal standard stock solution was made by dissolving 50 µL of acetone in 50 mL of solvent. Preparation of the sample solution was done as follows: 0.15 g of cream matrix was weighed and put into a headspace vial; then, 70 µL of internal standard was added up to 5 mL with the solvent and vortexed for a minute. The spiked sample solution was prepared using 0.15 g of cream matrix, formaldehyde standard solution, and 70 µL of internal standard stock solution. It was added to 5 mL by the solvent, then vortexed for a minute. The selectivity solutions were made by preparing standard solutions of formaldehyde, formic acid, n-hexane, cyclohexane, and acetone mixture in a concentration of 10 µL/mL of each dissolved with the solvent to 5 mL.

### Optimization Method 1 with 2,4-Dinitrophenylhydrazone Derivatization by HPLC-DAD

The optimizations were carried out as follows: first, column selection using nonpolar column 1 MS, 5 MS, and phenyl column 5 μm (250 mm×4.6 mm) was performed to observe the optimal separation between the peaks of the analyte and other compounds. Second, variations of acetone-trile and water composition in the mobile phase were made to provide the optimal peak analyte response. Third, the temperature and incubation time were modified by varying the temperature to 30, 40, 50, and 60 °C; and incubation time to 10, 20, 30, 40, 50, and 60 min. After that, these three optimizations were observed for the optimum area response in the spiked sample.

### Optimization Method 2 with p-Toluenesulfonic Acid in Ethanol Derivatization by GC-MS and GC-FID

The following optimizations were carried out: first, column selection using nonpolar column 1 MS, 5 MS, and polar wax column (poly(ethylene glycol) 100%) was made to observe the optimum separation between the peaks of the analyte and other compounds. Second, the temperature programmed of the mobile phase was optimized so that it could provide suitable parameters that meet the requirements and could provide consistent data at a fixed flow rate. Third, the temperature and incubation time were optimized by varying the temperature to 30, 40, 50, and 60 °C and incubation time to 10, 20, 30, 40, 50, and 60 min. Afterward, the optimum area response in the spiked sample was observed. Later, the optimization for determining the p-toluenesulfonic acid concentration in ethanol was done by using five concentrations: 0.1, 0.5, 1.0, 1.5, and 2.0%, and the peak response area in the spiked sample that gives the optimum area response was observed.

Table 1b. Intraday and Interday Precision Test Result by HPLC-DAD and GC-FID\(\textsuperscript{a}\)

| parameter | DNPH method HPLC-DAD | p-toluenesulfonic acid liquid GC-FID |
|-----------|-----------------------|-------------------------------------|
|           | day I                  | day II                             | day III                     |
| average (%) | 101.28               | 101.80                             | 101.90                     |
| SD        | 0.38                  | 0.43                               | 0.27                       |
| RSD (%)   | 0.37                  | 0.42                               | 0.27                       |
| Horwitz (%) | 5.32                 | 5.32                               | 5.32                       |
| Horrat    | 0.07                  | 0.08                               | 0.05                       |
| RSD (%) combined | 0.44             | 1.15                               | 98.59–102.61 |

\(\textsuperscript{a}\)DNPH (2,4-dinitrophenylhydrazine). HPLC-DAD (high-performance liquid chromatography-diode array detector). SHS-GC-MS (static headspace-gas chromatography-mass spectrometry). GC-FID (gas chromatography-flame ionization detection). RSD (relative standard deviation), Horwitz and Horrat: acceptance criteria of the accuracy and precision test (AOAC guidelines).
Method Validation. The validation parameters determined were selectivity or selectivity, linearity, range, limit of detection (LOD), limit of quantitation (LOQ), intraday and interday precision, accuracy, and robustness.7−9 The selectivity test was performed by injecting 1% p-toluenesulfonic acid in ethanol (solvent), cream matrix, formaldehyde standard, the spiked sample, internal standard acetone, and other compounds with similar physical and chemical properties as the impurity or degradation product that may be contained in cream cosmetic products such as n-hexane, cyclohexane, and formic acid solution. The retention time was analyzed from the resulted chromatogram. The acceptance requirement of the selectivity test was that there is no overlapped retention time that indicates interferences.

Linearity and range tests were done by injecting seven concentrations of the spiked sample into the gas chromatography system in three repetitions. The linear regression equation was obtained by plotting the concentration of formaldehyde to the ratio of the area of formaldehyde to the internal standard of acetone to obtain the line equation \( y = bx + a \). As parameters for analyzing the existence of a linear relationship, the correlation coefficient \( (r) \) and the regression function variation coefficient \( (V_{\text{rel}}) \) were used. The range is the limit of the lowest concentration value to the highest concentration with precision and accuracy that meets the requirements. LOD and LOQ were calculated statistically through the linear regression equation obtained.

Determination of the intraday precision using a spiked sample solution with a concentration of 100% was carried out six times. Interday precision was also determined using the same technique with six repetitions. The terms of acceptance were % RSD ≤ 3.7%, Horwitz ratio < 2.0%, and confidence interval (CI): 95−105%.

The accuracy test was performed through each of three series of concentrations (80, 100, 120%) injected three times. The analyte content was calculated by comparing the area ratio

| Table 2. Results of Accuracy and Intraday/Interday Precision for Three Concentration Levels Using the GC-MS Methoda (Revised) |
|---|---|---|---|---|---|
| concentration (μg/mL) | accuracy | precision | accuracy | precision | accuracy | precision |
| | (%recovery) | SD | RSD (%) | (%recovery) | SD | RSD (%) | (%recovery) | SD | RSD (%) |
| 5 | 100.30 | 1.17 | 1.16 | 100.62 | 0.79 | 0.79 | 101.44 | 0.37 | 0.36 |
| 10 | 100.90 | 0.74 | 0.73 | 100.73 | 0.96 | 0.95 | 100.81 | 0.20 | 0.20 |
| 15 | 100.19 | 0.16 | 0.16 | 100.10 | 0.05 | 0.05 | 100.69 | 0.09 | 0.09 |
| confidence interval (%) | 98.98−101.74 | 99.64−101.81 | 99.59−101.85 |

*aAcceptance criteria: %Recovery: 95−105%; RSD: 3.7% SD = standard deviation. RSD = relative standard deviation.

| Table 3. Relative Intensity (%) of Mass (m/z) by GC-MSa |
|---|---|---|
| % relative intensity of mass (m/z) | standard | spiked sample |
| | 59.0 (base peak) | 103.0 |
| name | 69.27% | 100.00% | 62.45% |
| standard | 67.51 | 100.00 | 62.73 |
| spiked sample | 67.17 | 65.79 |
| A | 68.64 | 64.14 |
| B | 66.75 | 64.41 |
| C | 65.27 | 63.36 |
| D | 66.22 | 60.31 |
| E | 65.87 | 62.73 |
| F | 65.27 | 63.36 |

*b% m/z (mass-to-charge ratio). GC-MS (gas chromatography-mass spectrometry). GC-EI-MS (gas chromatography-electron impact-mass spectrometry).

Figure 5. Mass spectrum of diethoxymethane (formaldehyde derivatization product) by GC-MS: (A) library; (B) standard solution 5 μg/mL; (C) spiked sample solution 5 μg/mL; and (D) cream cosmetic solution.
of formaldehyde and acetone to the theoretical formaldehyde and acetone ratio and the calculated accuracy (percent recovery).

Robustness was assessed by making slight changes to the method and evaluating the effectiveness of its relative standard deviation, which was changed to the split ratio of ±10% of the analysis method used. The robustness was obtained by making additional adjustments to the method and then evaluating the effect of its relative standard deviation. These adjustments were done as follows: first, the split ratio of ±10% of the analysis method used for GC-MS and GC-FID was changed from 1:25 to 1:23 and 1:27. Second, the flow rate from 1.0 mL/minute was adjusted to 0.8 mL/minute and 1.2 mL/minute for HPLC-DAD.

**Determination of Formaldehyde, Diazolidinyl Urea, and Imidazolidinyl Urea Concentration.** Determination of formaldehyde was made by weighing 150 mg of the homogenized samples and putting into a headspace vial and adding 70 μL of internal standard acetone and 5 mL of solvent. This process was carried out three times with each injection. The solution was also injected three times. The HPLC-DAD method was used to quantify the levels of diazolidinyl urea (DU) and imidazolidinyl urea (IU) as formaldehyde releasers in cream cosmetics.

**Determination of the Effect of Ethanol on the Concentration of Formaldehyde Released.** The effect of ethanol on the release of formaldehyde was analyzed by adding 5 mL of absolute ethanol into 10 g of the cream matrix and stirring the mixture homogeneously. An amount of 150 mg of the spiked matrix was weighed and dissolved in 5 mL of solvent, and the percent recovery was calculated.

## CONCLUSIONS

The analysis method of formaldehyde in the cream cosmetics products by static headspace GC-MS with derivatization techniques using p-toluenesulfonic acid in ethanol with internal standard acetone and the GC-FID liquid injection technique gave results that met the validation parameters of selectivity, accuracy (% recovery), precision, linearity, range, limit of detection, limit of quantitation, and robustness. Analysis of six cream cosmetic products with the validated PTS-GC-MS and DNPH-HPLC-DAD methods fulfilled the requirements for formaldehyde levels less than 0.2%, both of which showed levels ranging from 0.02 to 0.08%. However, the formaldehyde analyzed using the PTS-GC-FID method cannot be quantified because the level was less than its LOD and LOQ.

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**Author Contributions**

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit it to the current journal; gave final approval to the version to be

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Table 4. Results of Sample Analysis

| sample | preservative determination | formaldehyde determination |
|--------|----------------------------|----------------------------|
|        | HPLC-DAD | GC-MS | GC-FID | HPLC-DAD | GC-MS | GC-FID |
| C (%)  | SD        | RSD (%) | C (%)  | SD        | RSD (%) | C (%)  | SD        | RSD (%) |
| A      | DU: 0.49  | 0.006   | 1.30  | 0.02      | 0.0002   | 0.91  | 0.02      | 0.000095 | 0.50 n.q |
| B      | DU: 0.30  | 0.005   | 1.69  | 0.02      | 0.0003   | 1.62  | 0.02      | 0.000215 | 1.36 n.q |
| C      | DU: 0.46  | 0.002   | 0.46  | 0.06      | 0.0011   | 1.96  | 0.06      | 0.001171 | 1.98 n.q |
| D      | IU: 0.46  | 0.007   | 1.45  | 0.06      | 0.0006   | 1.01  | 0.08      | 0.001827 | 2.38 n.q |
| E      | IU: 0.40  | 0.006   | 1.59  | 0.03      | 0.0002   | 0.65  | 0.02      | 0.000511 | 2.78 n.q |
| F      | IU: 0.48  | 0.005   | 1.06  | 0.03      | 0.0001   | 0.43  | 0.04      | 0.000208 | 0.54 n.q |

“DU (diazolidinyl urea), IU (imidazolidinyl urea), C (concentration), HPLC-DAD (high-performance liquid chromatography-diode array detector), GC-MS (gas chromatography-mass spectrometry), GC-FID (gas chromatography-flame ionization detector), SD (standard deviation), RSD (relative standard deviation), n.q. (not quantified).

Table 5. Estimated Economic Value Comparison of the Three Methods

| no  | factor                   | HPLC-DAD | GC-MS | GC-FID |
|-----|--------------------------|----------|-------|--------|
| 1   | detector                 | IDR 300.000.000 | IDR 900.000.000 | IDR 400.000.000 |
| 2   | stationary phase          | IDR 10.000.000 | IDR 10.000.000 | IDR 10.000.000 |
| 3   | solvent price/L derivatizing agent/g | IDR 375.000 | IDR 200.000 | IDR 200.000 |
| 4   | time limit pre-order      | (N.A.) (6–8 weeks) | (6–8 weeks) |
| 5   | miscellaneous             | IDR 207.500 | IDR 127.200 | IDR 72.000 |
| 6   | gas/24 h time for preparation | 4–6 h | 1 h | 2 h |
| 7   | analysis time             | 30 min | 35 min | 35 min |
| 8   | instrument conditioning   | 6 h | 12 h | 12 h |
published; and agreed to be accountable for all aspects of the work.

Notes
The authors declare no competing financial interest.

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ABBREVIATIONS USED
PTS, p-toluenesulfonic; GC-MS, gas chromatography-mass spectrometry; GC-FID, gas chromatography-flame ionization detection; HPLC, high-performance liquid chromatography; DAD, diode array detector; SHS, static headspace; DNPH, 2,4-dinitrophenylhydrazine; DU, diazolidinyl urea; IU, imidazolidinyl urea; RSD, relative standard deviation; R, resolution; Rp, Indonesian rupiah.

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