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ANALYSIS AND VALIDATION OF DETECTION METHOD FOR ETHYLENE AND DIETHYLENE GLYCOL CONTAMINANTS IN SYRUP USING GCMS (GAS CHROMATOGRAPHY-MASS SPECTROMETER)

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ABSTRACT
Ethylene glycol (EG) and diethylene glycol (DEG) are hazardous compounds if ingested by the human body. Testing conducted by the Indonesian National Agency of Drug and Food Control (BPM) identified contamination of EG and DEG in glycerin and propylene glycol, which are utilized as solubility enhancers in syrup-based pharmaceuticals. This study aims to analyze EG and DEG contamination in children's syrup drug samples using a Gas Chromatography-Mass Spectrometry (GC-MS) instrument. This study presents an analytical method for detecting EG and DEG contamination. Based on BPOM regulations governing the control a determination of EG and DEG. Several syrup drug samples, which are listed in the BPOM drug withdrawal list under Number HM.01.1.2.11.22.240, were each weighed at 5 grams, transferred into a 50 mL volumetric flask, 30 mL of methanol was added, and the mixture was sonicated for 5 minutes. Subsequently, solvent was added up to the calibration mark. Five out of eight samples were found to contain EG and DEG at concentrations of less than 0.1%. Validation of the GCMS method for EG and DEG compounds yielded accuracy values with recovery rates between 98% and 101%. The acquisition test results produced a relative standard deviation (RSD) value of 0.87. The linearity test showed a correlation coefficient (r) of 0.955. The limit of detection (LOD) for EG was 0.26 ng/mg, and for DEG it was 0.51 ng/mg. The limit of quantification (LOQ) for EG was 0.86 ng/mg, and for DEG it was 1.69 ng/mg. This validation indicates that the analytical method exhibits high accuracy and sensitivity.

Keywords: Diethylene Glycol, Ethylene Glycol, GC-MS (Gass Chromatography-Mass Spectrometer), Drus

1. INTRODUCTION

In early October 2022, the World Health Organization (WHO) warned about four medicinal products classified as substandard medicines. When a medicinal product that has been registered with a licensing authority is found not to meet quality standards or product specifications or both, including exceeding contamination limits, it is classified as a "substandard medicinal product" or "out of specification product" (Baffi et al., 2000). The four medicinal products were in syrup form, manufactured by a pharmaceutical company in India, and licensed for cough indications. The incident started with a case report of acute renal impairment in 66 pediatric deaths in the Republic of The Gambia following the use of these products. Laboratory tests showed that the four products contained Ethylene Glycol (EG) and Diethylene Glycol (DEG) contaminants at levels exceeding the acceptable threshold of more than 1% (WHO, 2022).

The Indonesian Food and Drug Administration (BPOM) has officially banned using EG and DEG as solubility-enhancing excipients in all pediatric and adult syrup products. EG and DEG are dangerous compounds. If they enter the body, the maximum dose of 1,500 mg/kg of body weight can cause death. EG that is swallowed and enters the body is metabolized in the liver by enzymes. This process produces glycolic acid, which results in a buildup of acid and oxalic acid in the body. Oxalic acid is a compound that can cause damage to the kidneys (Peterson & Rodgerson, 1974). Meanwhile, DEG that enters the body will be processed in the liver into a compound 2-hydroxythoxyacetic acid (HEAA), which is very acidic and can damage the kidneys and nerves (Pérez et al., 2021). From January to October 18, 2022, 206 children experienced mysterious acute kidney disorders spread throughout Indonesia.

Although their use is prohibited, EG and DEG contamination can occur in other excipients used in drug formulations. Some excipients that have the potential to be contaminated are Glycerin and Propylene glycol. Glycerin and Propylene glycol are used as solubility enhancers for active ingredients in syrups and suspensions. Therefore, it is necessary to periodically test EG and DEG contamination levels using specific, accurate and sensitive analytical methods because syrup and suspension medicinal products contain other excipients that make it difficult to detect contamination levels (BPOM, 2022). The use of GCMS as an instrument for the detection analysis of a compound in a mixture has been widely developed. One of the GCMS methods in Jose J. Perez's research was to detect EG and DEG contamination in Propylene glycol, and Glycerin used as excipients in e-cigarettes. This research seeks to address this gap by evaluating the presence and levels of EG and DEG in children's syrup preparations, an area that has not been extensively explored before. GCMS offers several advantages, such as high efficacy and resolution whict enable it to accuractely analyze extremely small particles (Zhou et al., 2016).

Although the analysis of EG and DEG generally used with GCMS instrument, a study by Fulgencio in 2022 developed a rapid detection method for identifying EG and DEG using Near-Infrares Spectroscopy coupled with PLS-DA. This method was validated by performance matrics like false positive a false negative rate with the decision limit was 52mg/L and detetction capability was 106 mg/L (Fulgêncio et al., 2022). Another research using GCMS was developed for the quantification of D-pinitol in carob syrup samples and the result shows that D-pinitol also beneficial as a functional organic food compared to other plants (Christou et al., 2019). By utilizing advanced analytical techniques, this study provides new insights into the safety and quality control of pediatric medications. Despite the known risks of EG and DEG contamination, limited studies have validated analytical methods using GCMS for pediatric syrups in Indonesia. This study was conducted using GCMS instruments by BPOM guidelines through letter number B-SD.01.02.31.311.10.22.96 concerning Analytical Methods for Ethylene Glycol (EG) and Diethylene Glycol (DEG) Contamination Tests using validation parameters such as precision, accuracy, LOD and LOQ. Based on the background that has been described, this study aims to analyze EG and DEG contamination in children's syrup drug samples using Gas Chromatography-Mass Spectrometry (GC-MS).

2. METHODS

The materials used in this study are samples of drug syrup included in the drug withdrawal list by BPOM Number HM.01.1.2.11.22.240 and 2 samples of drugs on the market, Methanol p.a, stirring rod, 50 mL volumetric flask, 100 mL volumetric flask, analytical balance, drop pipette, Erlenmeyer flask, beaker glass, and 0.45 microliter filter membrane.

2.1. Methods Optimized GCMS Conditions

The optimized GCMS Agilent conditions are DB Wax UI column (or equivalent) 30 m long, 0.25 mm inner diameter, 0.25 µm film thickness containing Polyethylene glycol. Detector Mass Spectrometer, Injector temperature 250°C, Column temperature 100°C held for 1 minute,

Temperature increases 10 °C/minute to 130°C held for 7 minutes, Temperature increase 20°C/minute to 240°C held for 3 minutes, Ion Source 230°C, Interface 240°C. The mobile phase is ultra-pure helium, with a gas flow rate of 0.65 mL, a split ratio of 10:1, an injection volume of 1 microliter, and a solvent cut time of 4 minutes.

2.2. Sampel Preparation

Standard solutions of EG and DEG obtained from Sigma-Aldrich were prepared by carefully weighing approximately 100 mg each of EG and DEG, put in a 100 mL measured flask, added 50 mL of solvent, sonicated for 5 minutes, and diluted to the limit mark. Then, make a standard curve by dissolving 30, 40, 50, 60, and 70 uL of EG standard solution and as much as 60, 80, 100, 120, and 140 uL of DEG standard solution in a 5 mL measuring flask. The preparation sample test solution was prepared by weighing 5 grams of each sample, entering it into a 50 mL measuring flask, adding 30 mL of methanol, sonicated for 5 minutes, and then adding solvent to the limit. Each test solution and standard EG and DEG solution took one microliter to be injected into GCMS using the Helium mobile phase and DB wax UI column (**Figure 1**).

3. RESULTS AND DISCUSSION

Following the investigation results of 2022, BPOM issued Circular No. HM.01.1.2.11.22.240 on November 6, 2022, announcing the revocation of circulation permits for drug syrups produced by PT Yarindo Farmatama, PT Universal Pharmaceutical Industries, and PT Afi Farma. The statement indicated that these manufacturers used propylene glycol as a raw solvent, and the finished products were found to contain EG contamination levels above the allowed limit. Additionally, BPOM Circular No. HM.01.1.2.12.22.188, dated December 22, 2022, highlighted that several drug syrups from PT Ciubros Farma and PT Samco Farma had their distribution permits revoked due to EG and DEG contamination exceeding safe levels.

In terms of sample collection, there were challenges in obtaining samples as the products had already been removed from the market. From the list of withdrawn products, only a few samples were successfully acquired, mainly from PT Afi Farma. These samples were sourced from leftover stock from patients and from stock that had not yet been retrieved by the Pharmaceutical Wholesale Distributors (PBF). Besides using the withdrawn samples as per BPOM's circular, commercially available, safe cough syrup samples were also used as a reference in the EG and DEG contamination analysis.

Ethylene Glycol (EG) and Diethylene Glycol (DEG) compounds are among the causes of poisoning identified in several countries. On October 5, 2022, the World Health Organization (WHO) released Medical Product Alert No. 6/2022 information about Substandard (contaminated) paediatric medicines identified in the WHO region of Africa (WHO, 2022). EG and DEG compounds are toxic substances found as contaminants in Polyethylene glycol, Sorbitol Syrup, Glycerol, and Propylene glycol used as pharmaceutical excipients or as Food Additives (BTP). Ethylene Glycol (EG) and Diethylene Glycol (DEG) are two contaminants that can lead to a range of health issues in humans (Udagani & Ramesh, 2015; Perala et al., 2014).

These glycols may be found in pharmaceutical syrups made from glycerol, sorbitol, or polyethylene glycol. Ethylene glycol commonly used as an addictive in polyester production, containers based from PET and antifreeze (Li et al., 2015). In late 2022, multiple reports emerged from various countries about batches of cough, antipyretic, and antihistamine syrups containing harmful levels of EG and DEG, which raised concerns with the World Health Organization (WHO). From an analytical viewpoint, various methods for analyzing glycols in pharmaceuticals have been documented, with most of the research focused on the analysis of raw materials (Altamimy, et al 2024). In addition to using samples that have been withdrawn based on the BPOM circular, two samples of safe commercial cough syrups are also used as a comparison in the analysis of EG and DEG contamination identification. The samples used in this study used PG or

Propylene glycol and Sorbitol as additives. The maximum limit of EG and DEG contamination levels in a drug sample that uses Propylene glycol and sorbitol additives is no more than 0.1%.

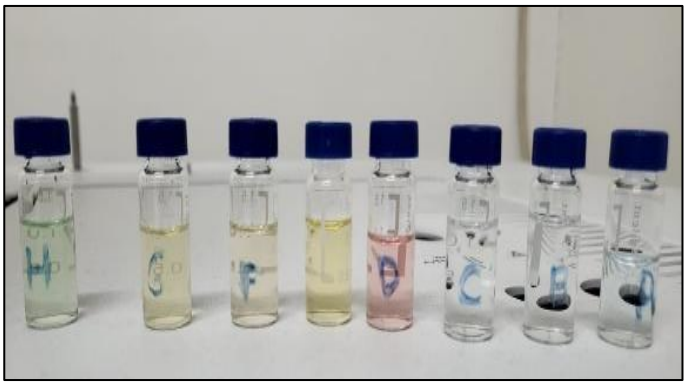

Figure 1. Samples used before injection into the GCMS

3.1. Methods of Validation

In a consider conducted by J. Orton in 2016, a simple Procedure was described for analyze of ethylene glycol, alcohol, methanol offering a low – cost approach using a liquid – liquid extraction. Thus, method does not require derivatization to achieve optimal results. This method was evaluated for precision, accuracy, reproducibility, linearity, selectivity, and limit of quantitation (LOQ), and was further correlated with existing GC methods, demonstrating accurate results (Orton et al., 2016).

Based on the figure's EG and DEG standard curves (**Figure 2**), the EG standard linear regression equation is obtained y = 2532x - 24784 with a value of r2 = 0.9855. At the same time, the DEG standard linear regression equation is y = 6480x - 72411 with a coefficient of determination of 0.9947. The linearity test is conducted to determine whether there is a significant linear relationship between one variable and another. This test is used as a requirement in linear regression or analysis. Linearity can be determined by creating a calibration curve, which involves preparing a range of standard solution concentrations and plotting the absorbance values against the standard concentrations. The concentration range used for EG and DEG is 15, 20, 25, 30, 35, 40, and 50 ppm.

Based on the standard curves of EG and DEG in **Figure 2**, the standard linear regression equation for EG is y = 2532x – 24784 with an r^2 value of 0.9855. Meanwhile, the standard linear regression equation for DEG is y = 6480x – 72411 with a coefficient of determination of 0.9947. The correlation coefficient value indicates the linearity or linear relationship between the concentration and its absorbance value. A good correlation coefficient value is one that approaches 1. The correlation coefficient value states the linearity or linear relationship the concentration produces with the absorption value. The accuracy test results obtained the average % recovery data at each concentration ranged from 98 - 101%, which is by the acceptance criteria of % recovery based on engagement according to AOAC for a concentration range of 10 ppm is 80 - 115% (AOAC).

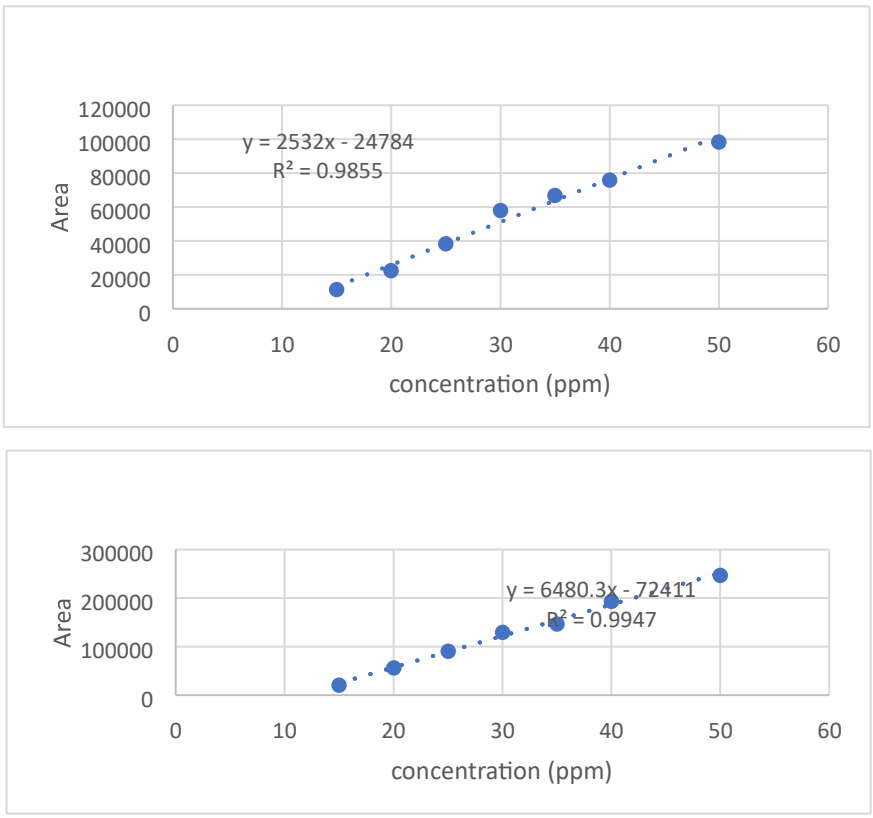

Figure 2. (a) the correlation absorbance and concentration of standard ethylene glycol (b) the correlation absorbance and concentration of standard diethylene glycol

The precision or accuracy test is conducted to measure the degree of closeness between the analytical results and the actual concentration of the analyte. Accuracy is measured as the percentage of recovery (% Recovery) of a certain amount of analyte added to the sample (Harmita, 2004). The accuracy test is conducted using a minimum of 9 determinations, which include 3 different concentration levels, with 3 replicates for each concentration. The concentration added to the blank should range from 80-120% (ICH, 2022). This study used 3 series of standard concentrations: low concentration (80%), medium (100%), and high (120%). The results of the accuracy test (**Table 1**) showed that the average % recovery for each concentration ranged from 98-101%, which is in accordance with the acceptance criteria for % recovery based on concentration, as per AOAC guidelines, where for a concentration range of 10 ppm, the acceptable range is 80-115% (AOAC).

Table 1. The result of accuracy

	Concentration (ppm)	Measured Concentration (ppm)	% recovery
Ethylene Glycol	8	8.01	100.125
	10	9.84	98.4
	12	11.89	99.08333
Diethylene Glycol	16	16.15	100.9375
	20	19.78	98.9
	24	24.15	100.625

Based on the EG standard calculations, the LOD value is 0.26 mg/L, and the LOQ value is 7.71 mg/L. At the same time, the analysis of LOD and LOQ for DEG is 0.51 mg/L and 1.69 mg/L, respectively. In other research by Altamimy 2024 that the value of LOD and LOQ were determined based on concentration levels where the signal-to-noise ratio exceeded 3 and 10, respectively. The LabSolution software was used to automatically calculate the signal-to-noise ratios. Six replicates of spiked samples were prepared at the LOQ, and the relative standard deviation (RSD) was computed. The acceptance criterion was set at an %RSD of less than 15%. LOQ for EG and DEG was estimated by the LabSolutions software to be 1 µg/mL, corresponding to a signal-to-noise ratio of >10 and an RSD of less than 15%. This value is equivalent to 25 µg/mL in the finished product. The LOD for each analyte was 400 ng/mL, which corresponds to a signal-tonoise ratio of >3. This is equivalent to 10 µg/mL in the finished drug product. (Altamimy, et al 2024). The RSD values obtained from the DEG and EG standards are 1.39% and 0.87%, which indicates precision was done carefully. When viewed from the AOAC reference, the precision acceptance (RSD) value for a concentration of 10 ppm is ≤ 6%.

In other study by Maurer in 2001, a GC-MS method was validated for the detection of EG and DEG contamination in human plasma with LOD and LOQ 0.01 g/L and 0.1g/L. Thus, method successfully differentiates specific plasma samples from urine patients (Maurer et al., 2001). In addition, in 2010 Holloway Gallina using GC with flame ionization detection (FID) for identification EG and DEG contaminants in glycerin-containing products. The result showed that Limit of detection are 0.0018% fro EG and 0.0036% for DEG (Holloway et al., 2010). Moreover in 2018 The measurement procedure for determination and limit value Quantification of EG and DEG was validated by Giesen et al. The limit quantification (LOQ) for EG and DEG are 0.5mg/L (Giesen et al., 2018). Beside from the previous study that the use of GCMS for detection and identification of EG and DEG contamination has been priven effective in the presence of EG and DEG from samples.

3.2. Content Analysis of Ethylene Glycol and Diethylene Glycol

Gas chromatography has a wide application, such that it can be used to separate and analyze several components. The **Figure 3** shows the chromatogram results of EG and DEG standards. Based on the analysis of the standard, the retention time is 2.063 in SIM scan mode for EG and 3.695 in the full scan mode for DEG. Method validation in chemical analysis consists of several laboratory experiments to ensure that the analytical methods used meet the established requirements (USP, 2009). Method validation on the study of EG and DEG in cough syrup needs to be done because of the different samples, and of course, the instrument conditions used are also different.

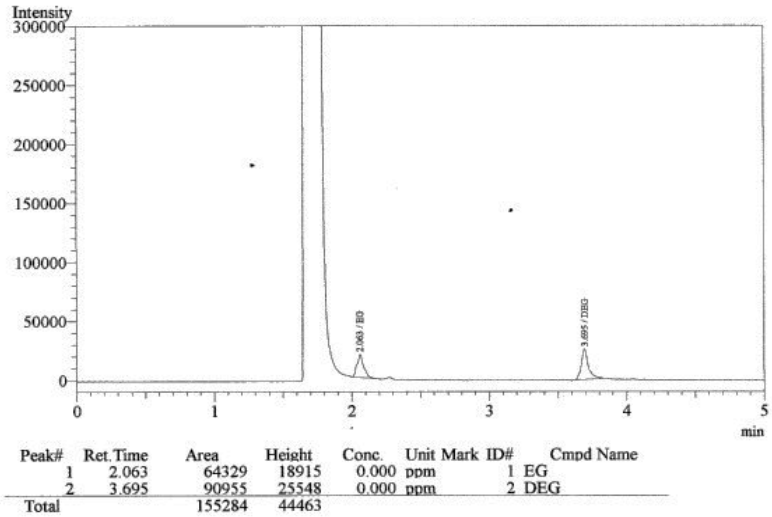

Figure 3. Mass spectrum results of EG and DEG standards

There were 5 out of 8 samples analyzed containing EG and DEG contamination, namely samples C, D, E, G and H. Samples C, D, and E are samples from drugs that were withdrawn because they contained EG and DEG contamination. In contrast, samples G and H are sold freely and included in the safe category by BPOM. Of the five samples, the EG and DEG contamination content is still in the safe category for consumption.

Table 2. Test results for EG and DEG contamination in medicinal syrup samples

The Sample	Test Results of EG and DEG
Sample A	N/A
Sample B	N/A
Sample C	DEG 0.0047 mg/mL
Sample D	EG 0.2318 mg/mL
Sample E	EG 0.8875 mg/mL
Sample F	N/A
Sample G	EG 0.0328 mg/mL
Sample H	EG 0.0465 mg/mL

Samples A-E are those that had been withdrawn by BPOM due to confirmed contamination with high levels of EG and DEG. The identification results are shown in **Table 2**, where out of the 8 samples tested, Sample C was found to contain DEG contamination with a concentration of 0.0318 mg/mL. Compared to the safe limit set by BPOM, this result is still within the safe consumption range. For all 5 samples, the levels of EG and DEG contamination remained within the safe consumption category, so they can be considered negative for harmful contamination (FDA, 2023).

The results were considered accurate and precise due to the method's linearity within the defined specifications. The detection limit of the method is lower than the allowable concentration of diethylene glycol in syrups and elixirs containing glycerin, highlighting the sensitivity of the method. This method's precision enables the detection of the maximum permissible concentration of diethylene glycol (0.1%) in pharmaceutical products for oral use. The statistical differences found when comparing the mean values of antipyretic and antianemic syrups were not practically significant. The polyvitaminic syrup group exhibited a consistent average (Baffi & Elneser 2000).

4. CONCLUSION

The experimental results showed that the optimum conditions were GCMS using a DB Wax column, ultra helium mobile phase, and MS SCAN and SIM modes. The results of the analysis of the EG and DEG contaminants contained in the samples were less than 0.1%, which is by the rules issued by the Indonesian Pharmacopeia VI and USP that the safe limit allowed is <0.1%. Given the severe health impacts of EG and DEG, especially in pediatric patients, it is strongly recommended that continuous monitoring and routine validation of pharmaceutical excipients such as glycerin and propylene glycol be conducted by manufacturers and regulatory authorities. Standardized GC-MS analytical protocols should be adopted widely to ensure reliable detection of contamination across different formulations and batches. Further research should focus on expanding sample coverage, including imported products and generics, and the development of rapid on-site screening methods to improve early detection and response. Integration of this method into regulatory quality control frameworks is crucial for improving public health safety and preventing future outbreaks of toxic contamination.

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6. CONFLICT OF INTEREST

All author declared that there was no conflict of interest.

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