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Development and validation of analytical method for ethanol content in medicinal cough syrup

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ABSTRACT
Cough syrup is a pharmaceutical preparation often containing ethanol as a solvent. However, the presence of ethanol in the drug can cause safety issues. This study aims to develop and validate a colorimetric method for determining ethanol in cough syrup. Cough syrup samples from different brands were analyzed using the method. The Visible spectrophotometric method uses the oxidation reaction of ethanol with potassium dichromate in an acidic condition. Method validation was conducted, including linearity, precision, accuracy, limit of detection (LOD), and limit of quantification (LOQ). The results showed this method had good linearity ($r > 0.99$) with a concentration range of 0.48 – 5.76 % (b/v). UV-Vis spectrophotometric method showed good precision and accuracy with SD = 0.0014, RSD = 0.4046 %, and % recovery = 99.99 %, while LOD = 0.1074 % and LOQ = 0.3253 %. This study concludes that the colorimetric method can be used as a valid and complementary method for analyzing ethanol content in cough syrup, providing important information for producers and consumers regarding product safety.

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Keywords
Analytical method validation, Cough syrup, Ethanol, Spectrophotometry.

INTRODUCTION

Ethanol is one of the commonly used pharmaceutical ingredients as a solvent in cough syrup. As an organic substance belonging to the chemical class of alcohol, ethanol has various physiological and pathological effects on the human body and its water-soluble properties (Farokhi & Ghayesh, 2018). The use of ethanol in pharmaceutical products, especially cough syrups, is a concern considering the relatively high prevalence of cough in the community. Studies show that 15% of children and 20% of adults report cough symptoms, with percentages reaching 60% in certain cases (Bergmann et al., 2021). Cough syrup is chosen as a form of preparation because of its ease of consumption, especially for patients with difficulty swallowing tablets. Syrup, a concentrated mixture of sugar and distilled water, often contains preservatives because it is susceptible to bacterial growth due to its high sugar content (Fickri, 2019). In addition, adding flavorings to syrup masks the unpleasant taste of prescription drugs (Kaushik et al., 2016). However, using ethanol in cough syrup requires close supervision, given the maximum concentration restrictions allowed, especially for products intended for children.

Regulations related to ethanol content in medicines set a maximum limit of 10% for products intended for adults and children aged 12 years and older, 5% for children aged 6 to 12 years, and 0.5%

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for children under six years of age (Chung et al., 2024). Furthermore, Pyart et al. (2020) emphasized that the ethanol concentration in the blood should not exceed 1 mg/100 ml for children under six years of age and 12.5 mg/100 ml for children aged 12 years and above. In response to these concerns, the Association of Paediatric Pharmacy released a List of KIDs in 2020, recommending a limit on ethanol content of no more than 5%. The European Medicines Agency (EMA) also published recommendations requiring explicitly indicating ethanol concentrations on drug packaging. Given the importance of controlling the ethanol content in syrup cough medicines, an accurate and reliable analysis method is needed. Two frequently used methods are UV-Vis Spectrophotometry and Gas Chromatography with a flame ionization detector (GC-FID). UV-Vis spectrophotometry is a simple, fast, and popular method for evaluating drug formulations in pharmaceutical laboratories (Dhobale et al., 2024). Although it has advantages for speed and ease of use, this method is more suitable for monitoring high ethanol concentrations due to its relatively low sensitivity.

This study uses a colorimeter instrument to develop an ethanol analysis method in syrup cough medicines. Validation of analysis methods includes evaluation of precision, linearity, limit of detection (LOD), limit of quantity (LOQ), and accuracy. By comparing the results of the analysis of the two methods, it is hoped that a more comprehensive understanding of the advantages and limitations of each method can be obtained, as well as recommendations for the selection of the most appropriate method in the context of analyzing ethanol levels in syrup cough medicines. The results of this study are expected to significantly contribute to the development of more accurate and efficient analysis methods for determining ethanol levels in pharmaceutical products, especially syrup cough medicines. In addition, the findings of this study can be a reference for the pharmaceutical industry and regulatory bodies in establishing stricter standards and testing protocols to ensure the safety of consumers, especially children, in the use of ethanol-containing syrup cough medicines.

RESEARCH METHOD

Materials

Cough syrup samples, distilled water (Brataco), concentrated sulfuric acid (Brataco), 96% ethanol (Brataco), potassium dichromate (Sigma Aldrich), sodium carbonate (Brataco), vaseline (Brataco). UV-Vis spectrophotometer (Shimadzu UV1900i, Japan), analytical balance (Shimadzu ATY 224R), Conway cup (CV. Nirvana Sains), glassware apparatus (iwaki pyrex).

Methods

1. Sampling

   Samples in this study were black cough medicine taken from random representatives from pharmacies without halal labels around the Special Region of Yogyakarta.
2. Sample preparation

   A total of 3 samples of cough syrup medicine with different brands were taken from various pharmacies. Each of the three samples was pipetted 5 mL to be dissolved into 15 mL, then put into a 50 mL volumetric flask and added with distilled water until the limit mark. The sampling method is purposive sampling or purposive sampling. Purposive sampling is a sampling technique with certain considerations or criteria. This study's criteria are cough syrups containing alcohol and come from various brands to validate the analytical method.
3. Preparation of reagent solution
   a. Standard solution

      The standard solution was prepared with six different concentration series from 96% absolute ethanol stock.
   b. Reagent solution

      Potassium dichromate ($K_2Cr_2O_7$) was weighed as much as 0.426 g and put into a 50 mL volumetric flask, then concentrated sulfuric acid (H_2SO_4) (Nahak et al., 2021).
4. Qualitative test
   a. Color Reaction using Potassium Dichromate ($K_2Cr_2O_7$)

      The potassium dichromate reaction test changed color from orange to green (Bahromi & Istianah, 2017; Kolo et al., 2022).

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b. Test with iodoform

The reaction test with iodoform showed the same results as the previous one, characterized by forming a yellow precipitate in the solution (Muchtaridi et al., 2012; Sari & Fajar, 2019).

c. Optimization of colorimetric method

This study's selection of the UV-Vis spectrophotometric method was based on several advantages (Kirchherr & Piscicelli, 2019). This method offers fast, sensitive, and relatively simple analysis for compounds that can absorb ultraviolet radiation or visible light. In addition, this method has wide applications in pharmaceutical analysis and is effective for quantifying various organic compounds, including ethanol.

5. Determination of maximum wavelength (λ)

The reaction solution between 1 series of ethanol content with dichromate solution in sulfuric acid was read for absorbance at a wavelength of 400-800 nm (Nahak et al., 2021).

6. Determination of operating time (OT)

The reaction solution between 1 series of ethanol levels with dichromate solution in sulfuric acid is read until the 30th-minute absorbance is read at the maximum wavelength until a stable absorbance is obtained (Shimpi, 2023).

7. Linearity

Ethanol standard solutions of concentrations 0.1, 0.2, 0.3: 0.4, 0.5, and 0.6% after being reconstituted with acid dichromate solution on a Conway dish then read the absorbance at the maximum wavelength and OT. The line equation y = bx + a was obtained (Nahak et al., 2021).

8. Parameter validation analysis method for determination of ethanol content using colorimeter instrument

a. Precision

The readings of the absorbance of the reaction result between ethanol and potassium dichromate solution from 6 replicate alcohol concentrations were calculated for the RSD value (Nahak et al., 2021).

b. Limit of detection and limit of quantitation (LOD & LOQ)

The limit of detection and quantitation with the UV-Vis Spectrophotometry method can be calculated statistically through the linear line of the standard curve (Nahak et al., 2021).

c. Accuracy

The absorbance reading results of the reaction between ethanol and potassium dichromate solution from adding 3 different alcohol concentration series and calculating the recovery value (Nahak et al., 2021).

9. Quantitative test

Eighteen samples of cough syrup were read by sampling with a validated Colorimetric method.

Data analysis

Data from determining the levels obtained were statistically tested with a homogeneity test. If the data is homogeneous, it is continued with a one-way analysis of variance (ANOVA) analysis with a confidence level of 95%. If there is a significant difference, it is continued with the BNT (Least Real Difference) test (Ostertagová & Ostertag, 2013).

RESULT AND DISCUSSION

In this study, qualitative and quantitative analysis was carried out using the colorimetric method to determine the alcohol content in cough syrup.

Quantitative analysis

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Qualitative analysis

Qualitative testing aims to determine the presence or absence of ethanol in the color reaction in the Potassium Dichromate test and iodoform reaction test. The presence of ethanol using potassium dichromate solution ($K_2Cr_2O_7$) + concentrated sulfuric acid solution (H_2SO_4) and using 0,1 N Sodium Hydroxide (NaOH) solution + iodine solution (I_2).

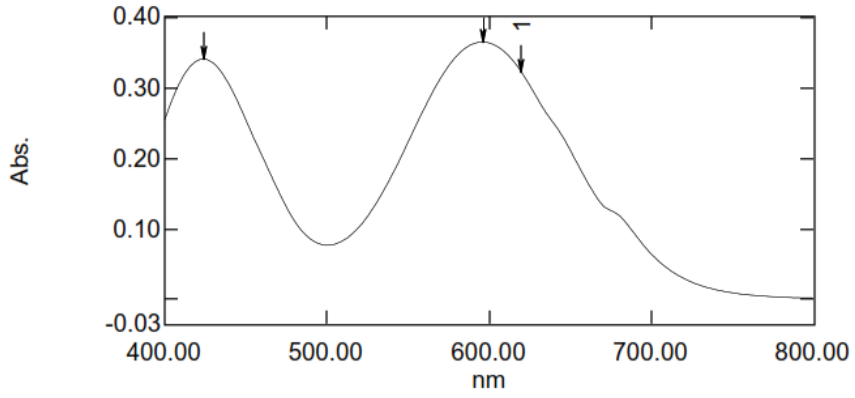
The principle is the redox reaction between ethanol and potassium dichromate ($K_2Cr_2O_7$) in an acidic condition. A positive test for ethanol in the sample is evidenced by the color change of potassium dichromate from orange to bluish-green (Kolo et al., 2022). Meanwhile, the solution was reacted with iodine solution (I_2); if there was an iodoform odor and a yellow precipitate formed within 30 minutes, this indicated the presence of ethanol in the sample. The yellow precipitate is an iodoform compound (CHI_3), resulting from the reaction between ethanol and iodine under alkaline conditions (Prakobdi & Saetear, 2023). So, the addition of potassium dichromate ($K_2Cr_2O_7$) reagent solution and iodine (I_2) reagent solution aims to provide qualitative confirmation of the presence of ethanol as a fermentation product produced in this study.

The qualitative test results of pure ethanol solution in cough syrup samples using potassium dichromate and iodoform reactions showed positive results. The oxidation reaction between the ethanol and the reagent results in a color change from orange to bluish-green, indicating the presence of ethanol in the sample. The reaction between ethanol, NaOH, and I_2 results in a brownish-orange discoloration and a yellowish precipitate, indicating the presence of ethanol.

Optimization of the colorimetric method

Before taking measurements on the quantitative analysis of ethanolic content, first determine the maximum wavelength of the acid dichromate solution, which aims to be an oxidizer that will oxidize ethanol into acetate (Sayyad et al., 2015). In determining the maximum wavelength, the absorption was measured in the wavelength range of 400-800 nm, obtaining a maximum wavelength of 596 nm where, at that wavelength, the compound undergoes changes in absorption for each unit of concentration is constant.

Maximum wavelength



No.	P/V	Wavelength nm.	Abs.	Description
1	↑	596.0	0.366	
2	↑	424.0	0.342	
3	↓	500.0	0.077	

Figure 1. Maximum wavelength of reaction ethanol and acidic potassium dichromate solution with ƛ max = 596 nm.

Determining the maximum wavelength aims to measure the change in absorbance for each unit of concentration that is greatest at the maximum wavelength so that maximum analytical sensitivity can be obtained (Tulandi et al., 2015). The wavelength of this study was determined by measuring the absorbance of ethanol with a dichromate solution in sulfuric acid at a wavelength of 400 nm-800 nm. From the results obtained, the maximum wavelength was 596 nm.

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Figure 1 on the graph shows the absorbance spectrum of ethanol and potassium dichromate solution in acid in the 400 – 800 nm wavelength range. An absorbance peak is seen at a wavelength of 596 nm, which is set as the maximum wavelength for subsequent analysis. In determining the maximum wavelength, a peak appears at 424 nm, the peak of potassium dichromate in an acidic condition that has not completely reacted with ethanol.

Operating time

Determination of operating time aims to determine the length of time required for the solution to reach constant absorbance (Tulandi et al., 2015). Optimization of the stability time is determined by measuring the absorbance of the ethanolic standard and potassium dichromate solution in sulfuric acid at the maximum wavelength of 596 nm with a time of 30 minutes using a Colorimeter. The research showed that the operating time after time optimization was up to minutes 0 – 15; after minutes 15, there was time instability. This operating time is determined by the research results of Shimpi (2023), which stated that the oxidation reaction between ethanol and potassium dichromate in an acidic atmosphere is stable for up to 30 minutes.

Standard curve (Linearity)

The standard curve (linearity) is obtained by plotting absorbance values with varying concentrations of standard solutions using the maximum wavelength. This curve is the relationship between absorbance and concentration. The calibration curve is a straight line if the Lambert-Beer law is fulfilled. In making this standard curve, the line equation obtained from the least squares method is used, namely y = bx + a; this equation will produce a correlation coefficient (r).

A good standard curve (linearity) (r > 0.99) obtained in this study indicates a proportional response between analyte concentration and measurement results within the range tested. This result aligns with (International Conference Harmonisation, 1994) Guidelines that set a standard correlation coefficient greater than 0.99 to validate analytical methods. This good linearity ensures the method's reliability in measuring ethanol content at various concentrations in cough syrup samples.

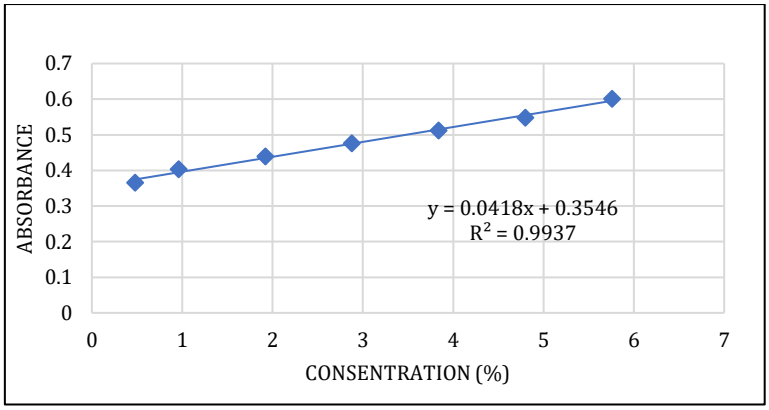

Figure 2. Linear regression of ethanol standard and potassium dichromate solution in various concentrations.

Figure 2 the graph shows the calibration curve for the ethanol standard, plotting the absorbance against concentration. A linear regression equation (y = 0.0418x + 0.3546) and correlation coefficient (R^2 = 0.9937) are shown, indicating the linearity of the method. Determining the standard curve (linearity) has the same purpose as the linearity validation parametric: to prove the existence of a linear relationship between the actual concentration and the method response. A standard solution of 96% ethanol with concentrations of 0.48, 0.96, 1.92, 2.88, 3.84, 4.80, and 5.76% was made; the absorbance was read using a UV-Vis Spectrophotometer with a wavelength of 596 nm. Then, a standard curve was made, and a slope value (b) of 0.0418, an intercept value (a) of 0.3546, and a correlation coefficient (R) of 0.9937 was obtained. This indicates that the standard curve (linearity) has a linear relationship

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between concentration and absorbance, according to the literature, the ideal linear relationship is achieved if R^2 = 0.99 to 1 (AOAC International, 2023).

Validation of the colorimetric method

Before proceeding to the quantitative testing of ethanol content in the sample, the first validation of the determination of ethanol was carried out with several validation parameters.

Precision

Precision is often measured as a percent Relative Standard Deviation (RSD) or Coefficient of Variation (CV) for several statistically significantly different samples. Precision criteria are given if the method CV value is 2% or less (Harmita, 2004). The first parameter is precision, which aims to prove the precision of a method based on the level of precision of individual analysis results indicated by the price of standard deviation (SD) and relative standard deviation (RSD). Based on the measurements' results, the standard deviation value is 0.0014, and the relative standard deviation value is 0.4045%. The standard deviation and relative standard deviation values are good if the SD value is < 2 and the RSD value is < 2% (Castilla-Polo et al., 2022). The results show that the method used has a good precision price, so it is feasible to determine ethanol content. Precision testing results can be seen in Table 1.

Table 1 contains the precision test results, showing absorbance values from six replicate measurements of a standard solution. It includes the mean, standard deviation (SD), and coefficient of variation (CV), which indicate the method's repeatability.

Table 1. Precision test result data of ethanol standard and potassium dichromate in sulfuric acid.

Replication	Absorbance
1	0.365
2	0.364
3	0.363
4	0.363
5	0.362
6	0.366
Mean	0.364
SD	0.0014
CV	0.4046%

Limit of detection (LOD) and limit of quantitation (LOQ)

After obtaining a calibration curve that meets the analysis requirements, the data obtained from the concentration of each analyte that gives different absorbance is processed to determine the limit of detection (LOD) and quantity (LOQ). In this study, the LOD price obtained was 0.11 %, which means that at this concentration, sample measurements can still be made, which provides a tool's accuracy based on the analysis results' accuracy. Meanwhile, the LOQ price of 0.32 % means that when measurements are taken, it can still provide analytical accuracy at that concentration.

Table 2. LOD & LOQ test result data of ethanol standard and potassium dichromate in sulfuric acid.

$\sum(Y-Yi)^2$	0.04
SD	0.08
LOD (%)	0.11
LOQ (%)	0.32

Table 2 presents the calculated values for the Limit of Detection (LOD) and Limit of Quantitation (LOQ) based on the calibration curve data. It includes the sum of squared residuals, standard deviation, and the resulting LOD and LOQ values in percent.

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Accuracy

Furthermore, the accuracy parameter aims to prove the closeness between the analysis results and the actual value. Accuracy is expressed as a percent recovery; the addition method is used in the accuracy test. In the addition method, the sample is analyzed, and then a certain amount of the analyte being examined (analyte/standard) is added to the sample and analyzed again. Based on the measurements' results, the average %recovery values were 99.85%, 99.86%, and 99.86% (Table 3), with a %recovery acceptance limit of 98%-102% (AOAC International, 2023). The value is acceptable because it is included in the acceptable range of 80%-120% (Castilla-Polo et al., 2022).

Table 3 displays the accuracy test results using the standard addition method. It shows absorbance values and calculated percent recoveries for three different concentration levels, along with the mean percent recovery and standard deviation for each level.

While the validation was primarily conducted using potassium dichromate in sulfuric acid rather than ethanol directly, this approach was chosen due to the nature of the reaction between ethanol and dichromate, which forms the basis of the detection method. The dichromate solution serves as a proxy for ethanol detection, as the absorbance of the reaction product is proportional to the ethanol concentration. This indirect method offers advantages in terms of stability and sensitivity, particularly for low ethanol concentrations in cough syrup samples. However, future studies could consider additional validation using standard ethanol solutions to enhance the method's robustness and directly represent the analyte of interest (Alahmad et al., 2022).

Table 3. Accuracy test result data of ethanol standard and potassium dichromate in sulfuric acid.

Concentration (µg/mL)	Absorbance	%recovery	Mean%recovery ± SD
80	0.351	99.57%	99.85% ± 0.28
	0.352	99.85%	
	0.353	100.14%	
100	0.356	99.58%	99.86% ± 0.28
	0.357	99.86%	
	0.358	100.14%	
120	0.361	99.59%	99.86% ± 0.27
	0.362	99.86%	
	0.363	100.14%	

Quantitative analysis

The quantitative test of determining the alcohol content of the sample was carried out, first measuring the absorbance of the blank (Sayyad et al., 2015), obtaining the blank absorbance of 1.013, then measuring the standard solution with a concentration of 0.5%, obtaining an absorbance value of 0.366. In measuring the sample solution, the triple method was used (measurement three times) with a wavelength of 596 nm. Based on the results of the quantitative analysis done using the colorimetric method, the alcohol content of cough syrup samples that had levels can be seen in Table 4.

Table 4 presents the results of quantitative analysis for alcohol content in six cough syrup samples (A, B, C, D, E, and F). It includes absorbance values from triplicate measurements, calculated ethanol content for each replicate, and the average alcohol content with standard deviation for each sample.

Based on information from Table 4, this result contradicts the provisions of (BPOM RI, 2016) Regarding quality standards for alcohol content in cough syrup. According to BPOM RI, the ethanol content should not be less than 30% b/v, while the analysis showed a much lower level (< 1%). From the results of this study, the cough syrup samples analyzed have lower alcohol content than the standard, which can affect the effectiveness and stability of the drug. However, the analysis showed lower ethanol content than the (BPOM RI, 2021). Interpreting these results requires careful consideration (Alzeer & Abou Hadeed, 2016). Pointed out that even low alcohol content can be problematic for consumers who are highly sensitive or have certain beliefs regarding alcohol consumption. Therefore, these results are not only relevant from a regulatory perspective but also have important implications for the social and religious aspects of drug consumption. The necessity for precise alcohol content analysis is further

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emphasized by studies showing a prevalence of over-the-counter medication misuse in certain populations (Treno et al., 2014).

Table 4. Quantitative Analysis of Samples.

Sample brand	Absorbance	Content (%)	Average level (%) ± SD
A	0.598	5.82	5.82 ± 0.06
	0.601	5.89	
	0.595	5.75	
B	0.548	4.63	4.62 ± 0.06
	0.551	4.69	
	0.545	4.55	
C	0.498	3.43	3.43 ± 0.06
	0.501	3.50	
	0.495	3.36	
D	0.448	2.23	2.23 ± 0.06
	0.451	2.31	
	0.445	2.16	
E	0.398	1.04	1.04 ± 0.07
	0.401	1.11	
	0.395	0.96	
F	0.372	0.42	0.41 ± 0.07
	0.375	0.48	
	0.369	0.34	

The conclusion of the ANOVA is a comparison of the significant price with the 95% confidence level. Before determining the ANOVA test, normality testing was carried out, resulting in values of 0.714, 0.972, and 0.972; the three samples had a significance value > 0.05, so the data were normally distributed. Furthermore, homogeneity testing was carried out, which resulted in a value of 0.405, with the three samples having a significance value of > 0.05, so the data variance was homogeneous. One way ANOVA testing produces a value of 0.000 is that there is a significant difference between the three samples analyzed. Then, to find out whether there is a significant difference between each sample, a further test or post hoc test is used with the BNT test, which results in a value of 0.000 that all samples have a significance value < 0.05 so that there is a real difference.

CONCLUSION

The UV-Vis spectrophotometric method with a wavelength of 596 nm meets the validation requirements of the analytical method for the determination of alcohol content in cough syrup. Precision, linearity, accuracy, and LOD & LOQ are validation parameters that meet the requirements. The results of determining the level of commercial cough syrup using this method for three samples, A, B, and C, resulted in levels of 0.43, 0.27, and 0.21%. This work contributes to improving medication safety and analysis in developing countries, an area identified as crucial for enhancing overall healthcare quality (Wallis et al., 2017).

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