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Analysis of Hydroquinone in Face Whitening Cream by UV-Vis Spectrophotometry and GC-MS Spectrometry

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Abstract

The analytical method to determine the compound content in both food and cosmetic products must be carried out carefully to ensure the validity of the analysis results. Hydroquinone has been widely found to be used as an active whitening agent in whitening cream. Technological advances have led to illegal whitening creams becoming more accessible online. This study aims to examine the hydroquinone content in the whitening samples cream purchased from e-commerce by various analytical methods, such as $FeCl_3$ reagent, cerimetric titration, UV-Vis spectrophotometry, and GC-MS spectrometer compared to the positive control hydroquinone. The results of the hydroquinone content by cerimetric titration and UV-Vis spectrophotometry methods were calculated quantitatively. Furthermore, the result compared through statistical tests showed a consistent hydroquinone content for both methods. Contrariwise, the GC-MS method showed negative results due to differences in the extraction process and solvent solubility. Based on the result obtained, can be concluded that all samples of whitening cream did not meet the requirements of BPOM No. 23 of 2019.

Keywords: Whitening creams, Hydroquinone, Cerimetry, UV-Vis Spectrophotometry, Gas Chromatography-mass spectrometry (GC-MS)

INTRODUCTION

Hydroquinone is a facial whitening agent that is widely used because of its effectiveness. The utilization of hydroquinone as a facial whitening agent has attracted controversy because it causes skin health problems such as ochronosis (Indriaty et al., 2018), irritation, extreme acne and other diseases (Mahé et al., 2003). Long-term use of hydroquinone also has the potential to cause cancer (Kooyers & Westerhof, 2006). One study showed that 8 out of 10 beauty cream samples containing hydroquinone at levels exceeding 2% were circulating in Alas District (Rahmadari et al., 2021). Furthermore, another study conducted in Jayapura showed that more than 2% hydroquinone was contained in 6 of 8 samples of whitening cream in circulation (Chakti et al., 2019).

Meanwhile, as many as 97 cosmetics containing prohibited and dangerous ingredients, dominated by hydroquinone, were discovered by BPOM and conveyed in a press release (Badan Pengawas Obat dan Makanan - Republik Indonesia, 2021). Based on several studies above, it can be seen that the use of hydroquinone in facial cream cosmetics is still found on a massive scale. On the other hand, development of technology and accessible e-commerce access cause the utilization of illegal face creams to become increasingly widespread.

Hydroquinone is a phenol group compound that is easily soluble in water, ethanol and ether (Depkes RI, 1995). Determining the concentrations of hydroquinone and other hazardous substances in cosmetic samples depends on the sample preparation stage and the analysis method used. The solvent elections as well as the right technique and method, will influence the results of the hydroquinone concentrations. Based on the method types, the hydroquinone analysis was carried out using qualitative and quantitative analysis. Thin layer chromatography (TLC) and color reaction methods are examples of qualitative analysis. Otherwise, the quantitative analysis can be carried out by the cerimetry titration method, UV-Vis spectrophotometry, high-performance liquid chromatography (HPLC), and gas chromatography–mass spectroscopy (GC-MS) (Suharyani et al., 2021).

Chromatography-mass spectrometry (GC-MS) is an analytical method that shows sensitive, precise,

and accurate performance. The sample is carried on to the gas phase, then the structure of the compound in the sample will be confirmed. GC-MS showed effective results when it was used to identify the presence of hydroquinone compounds in strawberry leaf samples that were extracted in methanol solvent. (Jurica et al., 2015). The weakness of this method is the high price of analysis. On the other hand, analysis of hydroquinone concentrations can be done using UV-Vis spectrophotometry. Hydroquinone can be analyzed using the UV-Vis spectrophotometric method because it absorbs radiation in the UV and visible regions due to the presence of a chromophore group (Arifiyana et al., 2019). This method is part of quantitative analysis techniques. Moreover, it shows faster analysis time and more affordable analysis costs compared to GC-MS analysis. Analysis of hydroquinone in the methanol solvent by UV-Vis spectrophotometry showed valid results (Rashid et al., 2022). Hence, it can be an option for a more affordable analysis method.

A glimpse of hydroquinone analysis was conducted in this study to examine appropriate methods and preparation techniques for whitening cream content analysis. Therefore, the hydroquinone concentration was carried out by both qualitative and quantitative analysis. It was conducted by $FeCl_3$ reagent, cerimetry titration, UV-Vis spectrophotometry analysis and GC-MS analysis.

METHODOLOGY

Materials and tools

The tools and instruments were gas chromatography-mass spectrometry, centrifuge, analytical balance, fume hood, AquaMate 8100 UV-Vis Spectrophotometer-Thermo Scientific, measuring flask, stir bar, spatula, separating funnel, burette, Erlenmeyer, volume pipette, and drop pipette.

Analysis of Hydroquinone by Reaction $FeCl_3$ Reagent

Six samples of facial whitening cream were obtained from one of the e-commerce stores and given codes A, B, C, D, E, and F as markers. 100 mg of the sample was dissolved in 5 mL of 96% ethanol and stirred until homogeneous. Each sample was added with five drops of $FeCl_3$. The green-to-black color change that occurs in the sample indicates that the sample is positive for containing hydroquinone (Chakti et al., 2019).

Analysis of Hydroquinone by Cerimetry Titration

Amount 20 mg of sample was dissolved in 30 mL of water and added with 10 mL of 0.01 N H_2SO_4 and five drops of diphenylamine, then titrated with 0.01 N cerium (IV) sulfate until a color change occurred. The violet/red color change that occurs in the final titration result indicates that the sample is positive for containing hydroquinone.

Analysis of Hydroquinone by UV-Vis Spectrophotometry

The standard hydroquinone solution was prepared by weighing 100 mg and then dissolving it with 96% ethanol. A standard solution of 1000 ppm hydroquinone in 96% ethanol was then diluted again to obtain a concentration of 100 ppm. The next stage is determining the maximum wavelength by measuring 15 ppm of standard solution at a wavelength of 200-400 nm. The highest absorbance is defined as the maximum wavelength. The procedure continued with determining the standard curve with concentrations of 3, 5, 7, 9, 11, and 13 ppm. Measurements using a UV-Vis spectrophotometer of whitening cream samples were carried out by weighing 500 mg of the sample, then adding 12 drops of 4 N HCl and 100 mL of 96% ethanol, stirring and then heating on a hot plate. The solution was then filtered by filter paper, which was filled with 1 g of sodium sulfate. The addition of sodium sulfate aims to attract the water phase in the sample. The resulting solution was then taken as much as 0.6 mL and diluted to 10 mL with 96% ethanol. The absorbance of each 3 mL was then measured using UV-Vis spectrophotometry at the maximum wavelength in triplicate.

Hydroquinone analysis with a GC-MS spectrometer

The whitening cream sample was weighed as much as 5 g, extracted in 50 mL of methanol and stirred until homogeneous. The positive control was hydroquinone. A centrifuge separates the solution. The 30 mL portion of the liquid obtained was placed in a separating funnel then, added with 30 mL of chloroform, then carried out by liquid-liquid extraction and then left to stand until the methanol and chloroform were separated. The chloroform solution obtained was then analyzed.

Data Analysis

Hydroquinone concentration that was analyzed by the cerimetry titration method was calculated using Equation 1 (Depkes RI, 1995).

$$\% \text{ content} = \frac{V\ Ce(SO4)2.4H2O\ x\ MCe(SO4)2.4H2O)2X\ BE\ Hydroquinone}{mg\ sample}\ x\ 100\% (1)$$

Hydroquinone concentrations that were analyzed by the UV-Vis spectrophotometric method were calculated based on the regression equation. It was obtained by determining the standard curve of the sample concentration versus the absorbance. Then, the hydroquinone concentration was calculated using Equation 2 and 3 (where y is the absorption value, a is the slope value (slope), b is the intercept value, while x is the concentration, V is sample volume, and Fd is dilution factor) (Rahmadari et al., 2021).

$$y = ax + b \quad (2)$$

$$\text{Hydroquinone content} = \frac{X \text{ x } V \text{ x } Fd}{\text{Sample weight}} \quad (3)$$

Moreover, the Hydroquinone concentration that was analyzed by GC-MS spectrometry method was carried out by observing the chromatogram containing the % area of the peak. Then, the hydroquinone concentration was recorded and listed in the table.

RESULTS AND DISCUSSION

Hydroquinone Content by Reaction of $FeCl_3$ Reagent

The $FeCl_3$ reagent can do the determination of phenolic compounds. Hydroquinone is a phenolic group. Therefore, the utilization of $FeCl_3$ in determining hydroquinone is appropriate. The black color that occurs when $FeCl_3$ is added is caused by the formation of complex compound phenyl alcohol ferrous chloride with hydroquinone in an acidic atmosphere. This complex compound is formed due to the presence of the phenolic -OH group. The reaction of $FeCl_3$ and hydroquinone in Equation 4 is an oxidation-reduction reaction (Musiam et al., 2019).

$$C_6H_6O_2 \text{ (hydroquinone)} + Fe^{3+} \rightarrow C_6H_4O_2 \text{ (quinone)} + Fe^{2+} \quad (4)$$

When 1% $FeCl_3$ reagent was applied to samples A, B, C, D, E, and F, the color changed to black, as did the positive control. Another study that utilizes $FeCl_3$ reagent shows a similar black color change. Based on these results, it can be predicted that the six whitening cream samples contain hydroquinone. The reaction of the whitening cream samples shows in Figure 1.

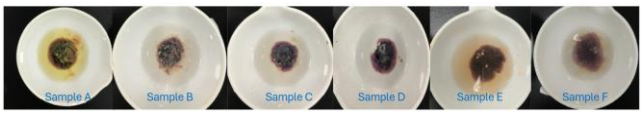

Figure 1. $FeCl_3$ reaction result with the samples

Hydroquinone Concentration by Cerimetry Titration

Cerimetry titration used cerium sulfate as a standard solution based on an oxidation-reduction reaction. Its technique is referred to as the Farmacope Indonesia Edition 4. Firstly, each whitening cream sample is dissolved and then added with indicator diphenylamine. Secondly, the mixture was then titrated by cerium sulfate. The color at the end of the titration is obtained from the addition of this indicator (Astuti et al., 2016). The purple color change is a sign of the endpoint (Depkes RI, 1995). Furthermore, positive controls were also titrated with a similar procedure. All results show the violet/red/purple color. Hydroquinone concentration in each sample and positive control are shown in Table 1. Meanwhile, the cerimetry titration result shows in Figure 3.

Table 1. Hydroquinone Analysis by Cerimetry Titration

Sample	Volume $Ce(SO_4)_2$	Hydroquinone content	Average	Parameter Criteria of BPOM
A	2.5 mL 2.3 mL	6.881% 6.330%	6.606%	TMS
B	2.1 mL 2.2 mL	5.780% 6.055%	5.917%	TMS
C	1.6 mL 1.6 mL	4.404% 4.404%	4.404%	TMS
D	2.0 mL 1.8 mL	5.505% 4.954%	5.229%	TMS
E	1.6 mL 1.3 mL	4.404% 3.578%	3.991%	TMS
F	0.5 mL 0.6 mL	1.376% 1.651%	1.513%	TMS
Positive Control (Pure Hydroquinone 5%)	23 mL 25 mL	5.064% 5.505%	5.285%	-
(Rapid Hydroquinone test kit)	3 mL 3.2 mL	1.270% 1.355%	1.313%	-

Note: Parameter: BPOM No 23 In 2019, hydroquinone in cosmetics should be 0%. TMS: Not eligible

Hydroquinone Analysis by UV-Vis Spectrophotometry

The maximum wavelength obtained was 293 nm, with an absorbance of 0.421. It is likewise Farmacope Indonesia 4th Edition, which mentions the absorption

spectrum of hydroquinone solution has a maximum wavelength of 293 nm (Depkes RI, 1995).

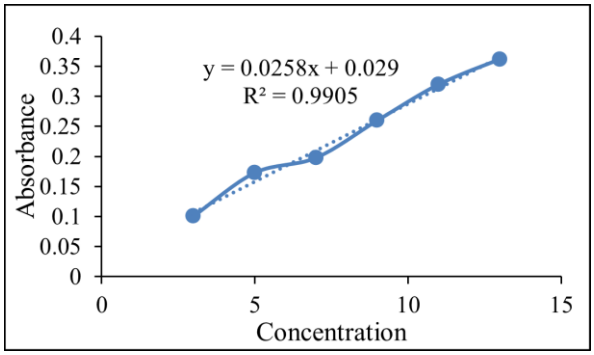

Figure 2. Standard curve of absorbance vs concentration

Table 2. Results of Hydroquinone Analysis using UV-Vis Spectrophotometry

Sample	Absorbance averge	Concentration (ppm)	Hydroquinone content	Parameter Criteria of BPOM
A	0.461	16.74	5.581%	TMS
B	0.457	16.59	5.531%	TMS
C	0.363	12.94	4.314%	TMS
D	0.358	12.75	4.250%	TMS
E	0.260	8.95	2.983%	TMS
F	0.106	2.98	0.993%	TMS
Positive Control (Pure Hydroquinone 5%)	0.256	8.79	5.868%	-
(Rapid Hydroquinone test kit)	0.585	21.55	2.763%	-

Note: Parameter: BPOM No 23 In 2019, hydroquinone in cosmetics should be 0%. TMS: Not eligible

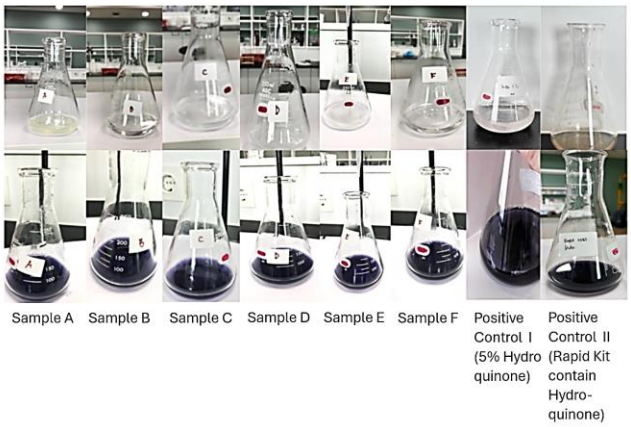

Figure 3. Cerimetry titration result

Figure 2 shows the absorbance versus the hydroquinone concentrations standard. The linear equation obtained from the standard curve is y = 0.0258x + 0.02 with a correlation coefficient r = 0.9905. The correlation coefficient (r) is a value used to determine the relation of the variables. The correlation coefficient (r) value obtained must be close to 1 to provide linear results. Hydroquinone concentration in the sample was calculated based on the absorbance, which was substituted into the linear equation. The hydroquinone concentration obtained by this method is shown in Table 2.

Hydroquinone Analysis by GC-MS

Analysis of hydroquinone in whitening cream was also carried out using a GC-MS spectrometer. In this method, there no hydroquinone content was found in the whitening cream samples. Nevertheless, other chemical compounds were found in the whitening cream samples. The chemical compounds found in the GC-MS results are selected based on the similarity index. The similarity index describes the similarity of the mass fragmentation of each component, which is matched based on the ion molecular weight, mass/charge (m/z) and the intense peak height contained in the NIST Database Library in the GC-MS Instrument. The analysis is based on the retention time that show by injected compound. Some factors such as temperature, pressure, mobile phase concentration and column dimensions, can influence the result. The similarity index category used is 70-99%. A higher similarity index number is considered a fragmentation peak in the gas chromatogram, so it can be indicated that the peak is identical to the compound read by the chromatogram. The fragmentation of the compound with the lowest molecular weight is selected as peak fragmentation analysis if a similar similarity index is found in the peak fragmentation (Asra, Rusdi, Arifin, & Nessa, 2019).

Based on the GC-MS results, two hazardous chemical compounds were found: pentachloroethane and hexachloroethane. Their utilization is prohibited in cosmetics based on BPOM Regulation No HK.03.1.23.08.11.07517 of 2011 (BPOM RI, 2011). Pentachloroethane is a colorless liquid with a sweet chlorine-like odor. This compound was found in samples A, C, D, E, and F, with the highest % area in sample F is 0.702%. This ingredient is prohibited for use in cosmetics because pentachloroethane is used as a solvent for oil and fat in the metal cleaning industry. Moreover, it is also used to separate coal from dirt, so its use in whitening cream is not recommended (Abdollahi & Behboudi, 2014).

Hexachloroethane (HCE) is a halogenated hydrocarbon consisting of six chlorines bound to ethane, which forms a white to pale yellow solid that is unstable in air and can evaporate gradually. The

hexachloroethane was found in samples A, B, C, E, F, and the positive control with the highest % area in the sample is 0.945%. The utilization of this compound is prohibited in cosmetics because of its use for industrial needs as an extreme pressure lubricant formulation, a chain transfer agent in emulsion polymerization, an anthelmintic in veterinary medicine, and a rubber accelerator. It is also used as a laboratory chemical as an ingredient in various fungicide and insecticide formulations. In addition, hexachloroethane has other uses, such as an ignition suppressant and as an inhibitor of methane explosion and ammonium perchlorate combustion (Ray & Burr, 2014).

Differences in analysis results

Several factors that can be considered for contrary results. In the study of determining hydroquinone analysis in whitening cream samples carried out by Chisvert et al., (2010), a silylation agent was added. The reaction of the silylation agent with hydroquinone will produce a hydroquinone derivative compound that is more volatile than the original hydroquinone compound. This process is known as the derivatization process. Moreover, the mass of the derivative compound is also greater and is more accurate when analyzed by mass spectroscopy in the GC-MS. The study results show that GC-MS is a valid method for analyzing hydroquinone from whitening cream samples. Hydroquinone derivatization was also carried out to improve the ability to separate compounds on GC-MS analysis (Dursunoğlu, Yuca, Güvenalp, Gözcü, & Yilmaz, 2018). Derivatization is also a procedure carried out to optimize the extraction process. The other optimization process can be carried out by the addition of ultrasonic and vortex in the preparation stage (Jurica et al., 2015).

In this research, no derivatization process was carried out. The sample was prepared with methanol and extracted by liquid-liquid extraction method, which uses chloroform as a solvent. The election of chloroform due to this solvent can evaporate easily in GC-MS operation. The extraction process has a weakness because the solubility of hydroquinone in chloroform is not too high (Kiss & Kunsági-Máté, 2019) (Jurica et al., 2015). The solubility of hydroquinone in some solvents is alcohol > ester > acetic acid > water (from high to low) (Li, Yin, Chen, & Wang, 2006). Furthermore, in the whitening cream formulation, there are ingredients such as emollients, surfactants, moisturizing agents, UV filters, softening agents, and other additional compounds that are also dissolved and can interfere with the extraction process. The extraction process was less optimal. It made the concentration of hydroquinone in the sample below the detection limit so that it was not detected. It was contrary to the positive control which shows a higher concentration of hydroquinone.

The analysis carried out by cerimetry titration and UV-Vis spectrophotometry had positive results for hydroquinone in all samples. Hydroquinone concentration obtained by UV-Vis spectrophotometry and cerimetry titration show insignificant differences. That indication is concluded based on data from the Significance Two Sided-p analysis, 0.453. Two-sided-p value = p-value = 0.453 > Alpha 0.05, where there is no significant difference between hydroquinone concentration in the analysis by the two methods. It is which shows consistent data. UV-Vis spectrophotometry has a lot of potential for interference from untargeted compounds, which also absorb similar UV-Vis wavelengths. For example, resorcinol has the same chemical structure as hydroquinone $C_6H_6O_2$ and the same molecular weight, namely 110.11 g/mol. The use of resorcinol in cosmetics is also prohibited, as stated in circular no PO.01.04.41.2237 (Badan Pengawas Obat dan Makanan-Republik Indonesia, 2021). The similarities between hydroquinone and resorcinol make it possible for the resorcinol compound to be detected in the UV-Vis spectrophotometry and cerimetry titration results. It can cause the analysis results between these two methods to have slight differences. In addition, although both methods are carried out in the liquid phase, the solubility of the resorcinol compound, which has similarities to hydroquinone, can also affect the endpoint of the titration if this compound is also contained in the test sample.

Hence, further studies must be carried out in the future using more appropriate preparation techniques and accurate and affordable methods. Moreover, it is necessary to add a positive control in the form of a whitening cream in which the exact concentration is known. That positive control cream can be formulated in the laboratory with various concentrations of other whitening agents and other ingredients that are generally used in cream formulations.

CONCLUSION

Overall, six whitening cream samples obtained from e-commerce that were analize by $FeCl_3$ reagent, cerimetry titration and UV-Vis spectrophotometry show that all samples were positive for containing hydroquinone. Hence, all whitening creams did not meet the requirements of BPOM No. 23 of 2019.

Nevertheless, analysis by a GC-MS showed negative results, contrary to other methods. Optimization of the extraction process and addition of control formulas of definite composition are needed to validate this analytical method for other cosmetic content determination.

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