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Detection and Determination of Captopril Using Silver Nanoparticles Based Colorimetric Method

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Abstract: Basic Health Research (Riskesdas) in 2018 showed an increase in the prevalence of hypertension in Indonesia. Captopril is one of the antihypertensive drugs that is often prescribed because it is affordable and effective in lowering blood pressure, but captopril also has several side effects. Therefore, the development of sensitive, simple, rapid and cost-effective analytical techniques for the determination of captopril is urgently needed. This research aims to develop a colorimetric detection of captopril using silver nanoparticles and analyze its performance in measuring the captopril in tablet samples. The parameters studied include linearity, sensitivity, accuracy and precision. The results of the research show that silver nanoparticles can be used for qualitative detection of captopril which is characterized by a color change and absorbance decrease of the sample solution. The results of the performance test of the developed method showed good results. The linearity test showed a correlation coefficient (r) of 0.9915 with the regression equation obtained was y = 0.263x + 129.26. The limit of detection (LOD) value is 0.0206 ppm and the limit of quantitation (LOQ) is 0.0687 ppm. In the accuracy test results, the recovery percentage (%recovery) was 95.3% and the precision test with the relative standard deviation (%RSD) obtained was 0.85%. The captopril content obtained in the 50 mg captopril tablet sample preparation was 98.0%.

Keywords: Captopril, Tablets, Colorimetry, Silver Nanoparticles

INTRODUCTION

Basic Health Research (Riskesdas) carried out by the Indonesian Ministry of Health in 2018 revealed a significant increase in the prevalence of hypertension in Indonesia's population of around 260 million people. This study found that the hypertension rate had increased to 34.1%, a big jump compared to the previous figure of 25.8% recorded in Riskesdas in 2013 (Kemenkes, 2018). One of the Angiotensin Converting Enzyme Inhibitor (ACEI) class of drugs that is widely prescribed as an antihypertensive is captopril. Captopril is indicated in patients after myocardial infarction, hypertension, diabetic nephropathy in patients with type 1 diabetes mellitus and in patients with heart failure. On the other hand, some side effects have also been reported if consuming this drug, such as dry and persistent cough, angioedema, stomach ache, constipation, dizziness, fatigue, etc (Hashemi *et al*., 2017).

Captopril in pharmaceutical formulations and biological samples has been widely measured using various methods and procedures such as using chromatography, spectrophotometry, fluorimetry, Raman spectroscopy, atomic absorption spectrometry, electrochemistry, volumetry and capillary electrophoresis. Captopril is widely used in various pharmaceutical products so that sensitive, simple, fast and cost-effective analytical techniques are needed for the determination of this drug. One of them is the colorimetric method. The colorimetric method uses color difference of standard and sample solution as an analytical signal[3]. The colorimetric method is easier and more practical because the measurement results can be observed visually based on color changes. In addition, the colorimetric method allows qualitative and quantitative analysis in real time measurement (Avissa & Alauhdin, 2022).

The colorimetric method can be carried out with the help of silver nanoparticles as a color change indicator so that detection is easy, the process is fast, and does not require complicated equipment. The use of Silver Nanoparticles has advantages over gold nanoparticles because of its superior optical quality. Silver also has good stability against light and heat and is more affordable (Dwistika & Suparno, 2018). Silver nanoparticles offer excellent optical sensing properties as they exhibit strong color with easy visualization of color changes.

METHODS

Material and Methods

Preparation of Silver Nanoparticles (AgNPs)

Preparation of AgNPs was carried out using the chemical reduction method, by mixing 27 mL of 1 mM silver nitrate solution with 3 mL of 1% sodium citrate. The mixture was heated at 70°C in a hot plate. During the heating process, stirring was carried out using a magnetic stirrer for 60 minutes so that the solution becomes homogeneous. Visually, the formation of AgNPs can be seen from the change in color of the reaction mixture from colorless to pale

yellow or brownish (Avissa & Alauhdin, 2022). The results in the form of AgNPs nanocolloids were then analyzed using UV-Vis spectrophotometer (Fluostar BMG Labtech) which was characterized by absorption at around 400 nm.

Colorimetric Detection of Captopril with AgNPs

The captopril solution was added to the AgNPs nanocolloid in a ratio of 1:2 (captopril solution: AgNPs nanocolloid). Each solution was photographed and analyzed for RGB (*red*, *green*, *blue*) values using the Color Detector application. Then a curve was created between the standard concentration (x) and the RGB value (y). From the curve, the equation y = bx + a and the correlation coefficient (r) will be obtained.

Detection of Captopril with AgNPs using UV-Vis Spectrophotometry

The captopril solution was added to the AgNPs nanocolloid in a ratio of 1:2 (captopril solution: AgNPs nanocolloid). The absorbance of the mixed solution was observed using a UV-Vis spectrophotometer at a wavelength of 300-600 nm. The AgNPs response to captopril is presented as Δabsorbance (ΔA), calculated using the following equation:

$$\Delta A = A_{\text{AgNPs}} - A_{\text{AgNPs}+captopril}$$

where:

Δ_{AgNPs} = Absorbance of AgNPs without captopril
$\Delta_{\text{AgNPs}+captopril}$ = Absorbance of AgNPs with captopril

Performance of AgNPs on Captopril Detection

The performance of silver nanoparticles in detecting captopril as a colorimetric sensor was tested based on the results of determining linearity, sensitivity, accuracy and precision. Linearity was measured over a range of concentrations 40, 60, 80, 100 and 120 ppm. Sensitivity was measured as the LOD and LOQ values of the standard deviation (σ) of the slope of the linearity plot. LOD is 3σ/slope, while LOQ is 10σ/slope. Accuracy was carried out using the standard addition method and the %recovery value was calculated. Precision was carried out using repeatability and the relative standard deviation (%RSD) was calculated.

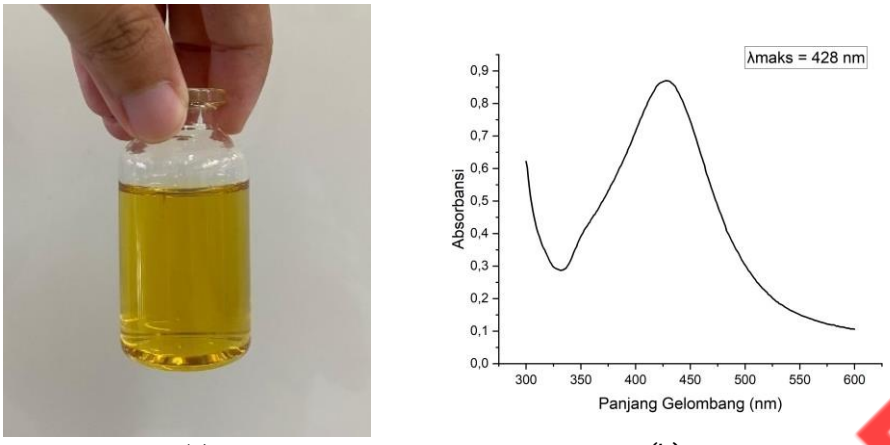
RESULT AND DISCUSSION

Synthesis of Silver Nanoparticles (AgNPs)

The synthesis of AgNPs in this research uses a chemical reduction method. The precursor material used is silver nitrate salt $AgNO_3$ and as a reducing agent is 1% sodium citrate which is also a stabilizing agent. The formation of silver nanoparticles occurs from Ag^+ ions on $AgNO_3$ which becomes uncharged (Ag^0). Ag^+ conversion to be Ag^0 through a reduction process by accepting electrons from donors. In this case, the reducing agent sodium citrate changes the Ag^+ silver ion solution into a colloidal solution of Ag^0 silver particles (Edityaningrum *et al*., 2022). Chemical reactions that occur:

$$4Ag^+ + C_6H_5O_7Na_3 + 2H_2O \rightarrow 4Ag^0 + C_6H_5O_7H_3 + 3Na^+ + H^+ + O_2$$

Initially the $AgNO_3$ solution clear in color, then changes to a brownish yellow color after gradual addition of sodium citrate (**Figure 1a**). This color change indicates that the reduction reaction has taken place and silver nanoparticles have been formed, which is indicated by the change in color of the solution to yellow as time increases. Silver nanoparticles (AgNPs) provide a distinctive color caused by plasmon absorbance on the silver surface[7]. The characteristic of silver nanoparticles is the appearance of an absorbance peak in the wavelength range of 400-450 nm which is a typical wavelength for silver nanoparticles (Prasetyaningtyas *et al*., 2020). Measurement results with a UV-Vis spectrophotometer on **Figure 1b** shows a maximum absorption peak at 428 nm. The results of characterization using PSA show that the overall average diameter of the silver nanoparticles that have been successfully synthesized is 34.9 nm. This is in accordance with the theory that a material is classified as a nanoparticle if it has a size of 1-100 nm.



(a) (b)

Figure 1. a) Synthesis Result of AgNPs; b) UV-Vis Spectrum of AgNPs

Colorimetric Detection of Captopril

The silver nanoparticles that have been successfully synthesized were then used for qualitative and quantitative detection of captopril using the colorimetric method. Detection of captopril with silver nanoparticles involves interactions between silver nanoparticles and thiol (-SH) groups which are part of the captopril structure. Compounds containing thiols can inhibit the catalyzing effect of nanoparticles (NPs) by forming NP-S covalent bonds and occupying the active site by replacing hydrogen cations (H^+) from the thiol groups[9]. The formation of these bonds causes aggregation, namely the formation of groups of particles through the collection of small particles by forming strong chemical bonds between the particles resulting in a decrease in the color intensity to pale yellow of the silver nanoparticles due to the presence of captopril. (**Figure 2**)

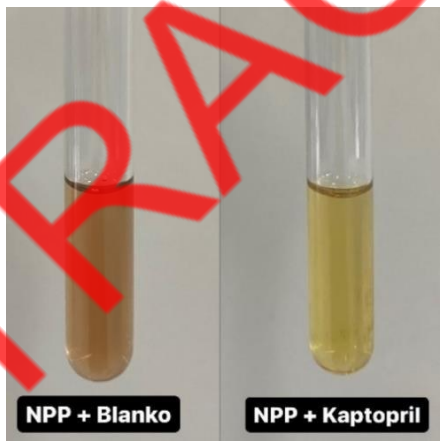
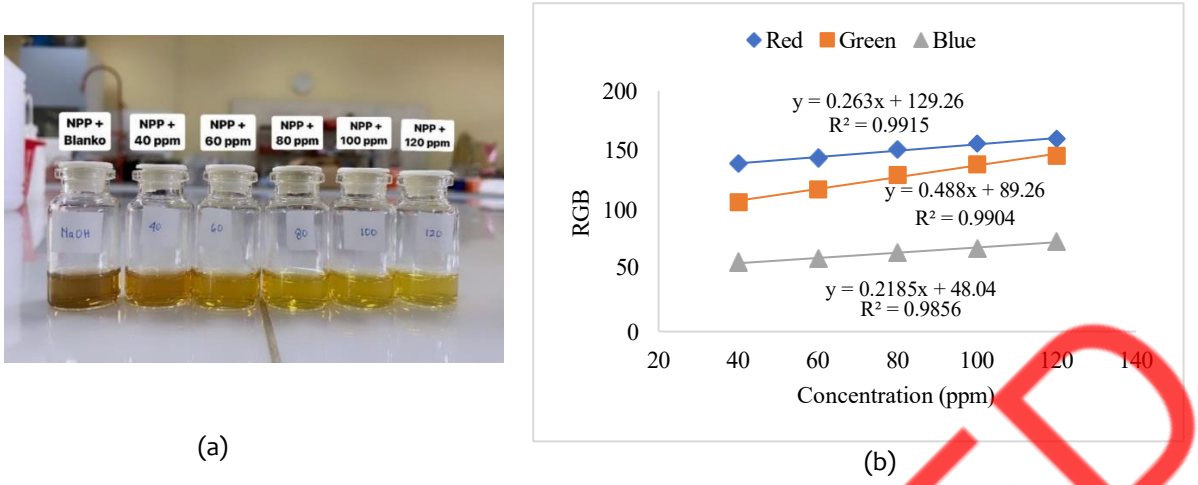


Figure 2. Colorimetric Test of Captopril with Silver Nanoparticles

Quantitative colorimetric analysis of captopril with AgNPs was carried out using the digital Color Detector application. This application was used to convert the color of the solution into Red, Green, Blue (RGB) values. Based on visual observation, the silver nanoparticle solution has a brownish yellow color, then after adding standard captopril solutions of various concentrations, the solution changes color to pale yellow as the concentration of captopril increases from concentrations of 40, 60, 80, 100 and 120 ppm as seen in **Figure 3a**. This color change occurs due to the aggregation of silver nanoparticles caused by the interaction of the sulfur in captopril with silver (Rastegarzadeh & Hasyemi, 2014). Each captopril standard solution was photographed under the same conditions and lighting to analyze the Red, Green, Blue (RGB) values using the Color Detector application, then the data were used to create standard curves. In **Figure 3b**, it can be seen from the correlation coefficient (r) that the most linear data is red (R) with correlation coefficient 0.9915. Then, the red standard curve data was used in the quantitative analysis.



(a) (b)

Figure 3. a) Captopril +AgNPs Standard Solution in NaOH; b) Captopril Standard Curve for Colorimetric Methods

Apart from the standard solution, the sample solution was also photographed under the same conditions as the standard solution. The Color Detector application was used to detect the RGB values of the solution and then calculate the levels using the standard curve that has been created. Based on the results of the analysis, the average level of captopril in the 50 mg captopril tablet sample was 98.0% (**Table 1**) which means it meets the requirements in the 2020 VI Edition of the Indonesian Pharmacopoeia which states that Captopril Tablets contain captopril, $C_9H_{15}NO_3S$, not less than 90.0 % and not more than 110.0% of the amount stated on the label (Kemenkes, 2020).

Table 1. Calculation of Captopril Content in Tablet Samples by Colorimetry

Replication	Sample Weight (mg)	Red Intensity	Volume (mL)	Dilution Factor	Concentration (ppm)	Percentage (%)
1	5002	140,9	50	20,83	44,26	92,2
2	5003	142,7	50	20,83	51,10	106,5
3	5000	141,3	50	20,83	45,78	95,4
			Average Percentage (%)			**98,0**

Performance of AgNPs in Captopril Detection

The linearity test was carried out from standard curve measurement data method. Linear regression analysis of the standard curve provides a correlation coefficient (r) value which indicates the linearity of the method. **Figure 3b** shows the results of the linearity test carried out resulting in linearity values for Red, Green, Blue which are in accordance with the 2001 BPOM requirements, namely a minimum linear regression of 0.98. However, among the three linear regressions, Red (R) data have the highest correlation coefficient (r) of 0.9915. It can be concluded that there is a linear relationship between concentration (x) and Δabsorbance (y), the higher the concentration, the higher the Δabsorbance produced, especially in the concentration ranges of 40, 60, 80, 100 and 120 ppm.

The sensitivity of the colorimetric method used for the analysis of captopril was evaluated using LOD & LOQ. The LOD is 0.0206 ppm, while the LOQ is 0.0687 ppm. In the meanwhile, accuracy was evaluated using present recovery. Captopril tablet samples were added to a standard captopril solution and persent recovery was measured. Based on **Table 2**, it is known that the persent recovery value for captopril analysis using colorimetric method was 95.3%. The persent recovery value obtained is acceptable because it follows the requirement in the range of 80%-120% so that the results can be stated to be accurate.

The precision value in the repeatability category was determined by calculating the relative standard deviation (RSD). Is the test was carried out 6 times by one analyst in a certain period. From the results of these test, the RSD value for the captopril tablet sample was 0.85% with a standard deviation (SD) of 0.44%. According to the Association of Official Analytical Chemists, a precision method is good if the relative standard deviation value is ≤ 2%. Therefore, the RSD percentage obtained shows that the developed method has high precision.

Table 2. Comparison of the Performance of Silver Nanoparticles in Detecting the Captopril

Parameter	Colorimetry	Spektro UV-Vis
Linearity	0,9915	0,9915
LOD	0,021 ppm	0,038 ppm
LOQ	0,069 ppm	0,127 ppm
Accuracy (%*recovery*)	95,3%	92,2%
Precision (%RSD)	0,853%	0,004%
Concentration of captopril in the sample (%)	98,0%	97,2%

Comparison of Detection of Captopril with AgNPs by Colorimetry and UV-Vis Spectrophotometry

The linearity results of captopril analysis using colorimetry and UV-Vis spectrophotometry produced the same correlation coefficient value of 0.9915, which means both have fulfilled the 2001 BPOM requirements. In this study, it can be concluded that there is a relationship between concentration and absorbance because the two methods used show good correlation values. The LOD and LOQ values in the analysis of captopril using the colorimetric and UV-Vis spectrophotometric methods produce different values. Using the colorimetric method, the LOD and LOQ results were respectively 0.021 and 0.069 ppm, while using the UV-Vis spectrophotometric method they were 0.038 and 0.127 ppm. Differences in results can be caused by different tool characteristics and working principles. Based on the data, it can be concluded that the use of the colorimetric method has better sensitivity than the UV-Vis spectrophotometric method.

The accuracy results for captopril analysis using the colorimetric and UV-Vis spectrophotometric methods were 95.3% and 92.2%, respectively. Both methods provide accurate and acceptable results as they are in the acceptance range of 80-120% (Muslich *et al*., 2020). However, if the two are compared, the colorimetric method has higher accuracy and will provide measurement results that are closer to the actual value. The precision value for the colorimetric method is 0.853%, while for the UV-Vis spectrophotometric method is 0.004%. Both methods showed very good precision results because the relative standard deviation value is ≤ 2%. However, the precision of the UV-Vis spectrophotometric method is better than the colorimetric method. The UV-Vis spectrophotometry measures absorbance at specific wavelengths whereas the colorimetric method only based on the color intensity measurement of the sample solution.

Analysis of captopril in tablet preparations using colorimetric and UV-Vis spectrophotometric methods produced levels of 98.0% and 97.2% respectively. Thus, the results obtained by both methods are in accordance with the requirements of the Indonesian Pharmacopeia Edition VI 2020 which states that Captopril Tablets contain captopril, $C_9H_{15}NO_3S$, not less than 90.0% and not more than 110.0% of the amount stated on the label. It can be concluded that the analysis of captopril using the colorimetric method and UV-Vis spectrophotometry has good performance for the detection of captopril with silver nanoparticles, but the use of the colorimetric method is simpler, cheaper, faster and easier.

CONCLUSION

Based on the results, it can be concluded that silver nanoparticles can be used for qualitative detection of captopril which is characterized by a decrease in absorbance and color intensity. The performance of silver nanoparticles in detecting the presence of captopril in tablet samples colorimetrically showed good results through linearity, limit of detection (LOD) and limit of quantitation (LOQ), accuracy and precision. The linearity test results show a correlation coefficient (r) of 0.9915 with a detection limit of 0.0206 ppm and a quantitation limit of 0.0687 ppm. In the accuracy test results, the recovery percentage was 95.3% and the precision test with the relative standard deviation (RSD) percentage obtained was 0.85%. Colorimetric detection of captopril with silver nanoparticles is simpler, cheaper and faster than the UV-Vis spectrophotometric method, and the sensitivity and accuracy are even better.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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