Review:

Strategies in Improving Sensitivity of Colorimetry Sensor Based on Silver Nanoparticles in Chemical and Biological Samples

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Abstract: *Colorimetric sensors-based silver nanoparticles (AgNPs) are very interesting to be studied and developed because of the simplicity and ease in the principle of detection. It does not require sophisticated and affordable tools but still has high sensitivity. The coefficient extinction of AgNPs is relatively higher than AuNPs of the same size, making the sensitivity of AgNPs higher than AuNPs. The principle of detection is based on the aggregation of nanoparticles with analytes that causes shifting in Localized Surface Plasmon Resonance (LSPR) to a larger wavelength, commonly called a bathochromic shift or redshift. It is a favorite phenomenon because it is more easily observed with naked eyes. This sensor shows a good analytic performance with high sensitivity due to strong LSPR and good strategies that selectively bring interaction between analytes and AgNPs. AgNPs are characterized using UV-Visible (Ultra Violet-Visible), TEM (Transmission Electron Microscope), FTIR (Fourier Transform Infrared), and DLS (Dynamic Light Scattering), and many analytes have been detected with this sensor successfully. This article discusses several important parameters in increasing the sensitivity of AgNPs colorimetric sensors. Finally, it can be used as guidelines in the development of methods in the future.*

Keywords: *sensitivity; colorimetric sensor; AgNPs; aggregation; bathochromic*

■ INTRODUCTION

The methods development for detecting organic or inorganic target molecules in chemical and biological samples have been widely reported. Those methods have been applied in many types of samples as follows: urine [1-5], blood plasma [2,4,6-8], water [9-13], food [14], drink [11,13,15-16] and drugs [7,17-23]. Several strategies have been implemented to produce sensitive, selective, effective, and efficient methods. However, many methods require sophisticated instruments such as HPLC, GC-MS, LC-MS, ICP-MS, or DNA-based methods [24] and need special techniques for sample preparation. Thus, this makes these methods less effective and efficient.

De Oliveira and de Sequira [25] monitored acetone levels in 207 workers' urine exposed to acetone/isopropanol at work and the detection of diseases related to lipid metabolism disorders. Quantitative analysis was performed using the headspace/gas chromatography method. The result showed that the mean acetone level was 1.12 ± 0.47 mg/L with a measurement range of 0.20–1.95 mg/L [25]. Teerlink [26] analyzed arginine residues, dimethylarginine asymmetry (ADMA), which is a nitric oxide synthase inhibitor and is suspected to be a signal of endothelial dysfunction in cardiovascular disease using the High-Performance Liquid Chromatography (HPLC) method. Sample preparation involved the solid-phase extraction method in a column cation exchanger [26]. Tebani et al. [27] analyzed sialic acid using the Liquid Chromatography-Tandem Mass Spectrometry

(LC-MS/MS) method [27], and Shimelis et al. [28] analyzed melamine using the Gas Chromatography-Mass Spectrometry (GC-MS) method [28].

Among various analytical methods, the colorimetric method is often preferred because of its simplicity and affordable cost [29]. The colorimetric method is a solution-based on color changes method that can be observed by the naked eye [3,15]. Traditionally, this method is based on the reaction between organic dyes and the analyte. However, the low extinction coefficient of organic dyes makes them less sensitive. Colorimetric sensors can also be performed based on diazotization reactions [30], complexation [31], redox reactions [31], enzymatic [32], and metal nanoparticles [33].

In recent years, some analytical methods that use metal nanoparticles have been developed. Metal nanoparticles are attractive because of their unique physical and chemical properties such as electrical, magnetic, optical, ionization potential, and catalytic [34]. Colorimetric sensors based on metal nanoparticles are widely chosen because of their unique characteristic, i.e., have Localized Surface Plasmon Resonance (LSPR) in the visible light area [29,35]. LSPR is a phenomenon exhibited by metal nanoparticles due to the presence of a plasmon absorption band when the photon frequency (electromagnetic radiation) resonates with the natural frequency of electrons on the surface against the positive nuclear return force [36]. For example, because of LSPR, gold nanoparticles (AuNps) have a high molar extinction coefficient (example: 2.7×10^8 $M^{-1}cm^{-1}$ for 13 nm AuNps) and have a limit of detection in the nanomolar range. Colorimetry applications based on metal nanoparticles have been widely used in detecting proteins, DNA, anions, metal ions, and organic molecules [29,35,37] in various samples. Precious metals that are often used are gold and silver [38-40]. The application of AuNPs is indeed very wide because of their stability compared to silver nanoparticles (AgNPs). However, due to high precursor prices and more complicated synthesis methods, AgNPs are widely chosen because they have a relatively higher extinction coefficient than AuNPs of the same size [11,19], resulting in high visibility and increased sensitivity.

The colorimetric principle is based on the aggregation of nanoparticles with analytes [4-5,8,21], causing LSPR to shift to a larger wavelength which is commonly referred to as a bathochromic or redshift. It is a favorite phenomenon because easier to observe with the naked eye. Usually, the AgNPs sensor will show a decrease in the absorption band at 400 nm but increases at 530 nm [23]. The principle of plasmonic sensors is to decrease particle distance, leading to a stronger plasmon coupling between nearby particles induced by aggregation. Nanoparticle aggregation showed an increase in particle size [11,41-42]. For example, cysteine induced the aggregation of AgNPs coated with fluorosurfactant anionic ligands due to electrostatic interactions [4]. There are two different aggregation mechanisms, namely: (1) aggregation with a crosslinking mechanism in the presence of a crosslinking molecule, which forms a bond area from nanoparticles to the target molecule, and (2) a mechanism without crosslinking molecules, where the target molecules such as DNA and peptides act as coagulants or stabilizer of nanoparticles [43]. The aggregation of nanoparticles can be caused by various factors such as pH, temperature, salt, and molecular charge [44]. Besides, the selection of reagents in complex modification, organic ligands, the addition of characterization tools, and the preparation of nanoparticles that require a long time are also factors that reduce sensor sensitivity.

AgNPs are visually yellow and have an absorption band of about 400 nm [39]. AgNPs applications have been widely used in various chemical and biological samples. In the biological sample, a silver nanoparticle that was modified with chitosan was used to detect sialic acid in blood serum with the linearity range is 0.007–0.57 mM and LOD is 0.009 mM [8]. Chen et al. [4] also used silver nanoparticles for colorimetric detection of cysteine in a urine sample that had a result of the linearity range, and LOD is 1.5–6.0 μM and 0.05 μM, respectively. In chemical samples, silver nanoparticles use to detect melamine in the milk sample and result in the linearity range, and LOD is 0.1–4 μM and 0.05 μM, respectively [16]. Also, silver nanoparticles modified

1,3-alternatecalix[4]aren used to detect Cu^{2+} ions in a water sample, with the result of LOD and LOQ being 2.5 × 10^{-6} M and 1 × 10^{-6} M, respectively, and this method is selective for Cu^{2+} ion [42]. Velugula and Chinta [23], to increase the sensitivity of silver nanoparticles for arginine detection in sample tablets, are modified with the Zn(II) Complex of Terpyridine. From this research, the linear range is 0.1–4.0 μM and 4–12 μM also LOD and LOQ are 2 μM and 200 ± 15 μM, respectively [23].

Silver nanoparticles are the ideal inorganic chromosphere due to their outstanding photophysical and photochemical properties. So AgNPs are often designed for colorimetric sensing systems. Moreover, the determination of analytes with AgNPs can be carried out with the naked eye without the need for sophisticated equipment and complex procedures [45]. However, the disadvantage of this AgNPs-based colorimetric sensor is poor sensitivity due to its susceptibility to surface oxidation, so surface functionalization plays an important role in enhancing the stability and analytical application of AgNPs [36]. Surface modification of silver nanoparticles is one way to increase stability. One of them can be used as an organic ligand that has an amine group (–NH_2) such as chitosan [2,8], melamine [9,13], and a thiol group (–SH) such as cysteamine [16] and L-cysteine. [14,33], which will interact with the target molecule through hydrogen bonding or electrostatic interactions [2].

Besides, errors in choosing the AgNPs synthesis method, incorrect optimization of parameters, and inadequate knowledge of the matrices contained in the sample can also reduce sensor sensitivity. So, efforts are needed to increase the sensitivity of the AgNPs colorimetric sensor, and the development of applications for various analytes in various samples can be continuous. This article summarizes the various strategies and efforts to improve the stability and sensitivity of AgNPs-based colorimetric sensors, both modified and unmodified. Also, it provides an overview of several important parameters in the design of the AgNPs colorimetric sensor. Furthermore, it describes the method that is often used, namely the method of reduction with reducing agents in the synthesis of AgNPs and provides several predictive schemes of the binding process of AgNPs with analytes that induce aggregation. And in the end, it can serve as a new challenge and direction for future research.

■ SYNTHESIS OF SILVER NANOPARTICLES

There have been many reports on nanoparticle synthesis methods, both the top-down approach (in physics) and the bottom-up approach (in chemistry). Much effort has also been made in synthesizing AgNPs to control size, shape, solubility, stability, and functionality. Synthesis of AgNPs has been widely reported using the bottom-up approach based on a reduction reaction, namely a change from Ag^+ ions to Ag^0 atoms. The selection of the right reducing agent affects the synthesized AgNPs both in terms of size and stability.

Chemical Reduction with Sodium Borohydrate ($NaBH_4$)

The chemical reduction of Ag^+ with sodium borohydride is commonly known as the Creighton method and was published in 1978 by J. Alan Creighton. Until now, many researchers have adopted this method for research development in AgNPs-based analysis. This method uses the $AgNO_3$ salt precursor and produces a bright yellow colloid solution. The reduction is:

$$AgNO_3 + NaBH_4 \rightarrow Ag^0 + 1/2H_2 + 1/2B_2H_6 + NaNO_3 \quad (1)$$

This method produces AgNPs particles with a size of about 12 ± 2 nm, with the absorption of a plasmon in an area of about 400 nm and a half-peak width or Full Width at Half Maxima (FWHM) of 50–70 nm [46].

■ STRATEGIES FOR IMPROVING COLORIMETRY SENSOR SENSITIVITY AND STABILITY MODIFICATION OF THE AgNPs SURFACE

Modification of AgNPs with Citrate

The Creighton method, with a few modifications, is mostly done with the addition of citrate. Citric acid can act as a reducing agent and stabilizer for AgNPs. This synthesis procedure results in a stable suspension of AgNPs for several hours under ambient conditions (23–25 °C) or days (at 4 °C), so long as it is protected from light [9] and resulting in a pale yellow solution [47].

Laliwala et al. [21] study demonstrated the characterization of yellow AgNPs-citrate that is used to detect four triptan family drugs in a drug sample with a maximum wavelength of 396 nm. Meanwhile, Chavada et al. [7] studied silver nanoparticles for the detection of Azithromycin in pharmaceutical and human plasma samples and showed the results of TEM AgNPs with a size of 12 nm with a bright yellow solution. Citrate coats the surface of the AgNPs with a negative charge. This causes electrostatic repulsion between adjacent particles and prevents aggregates. The optical properties of AgNPs-citrate also depend on the size and shape, and the most important is the particle distance particles. The positive charge from other molecules can easily interact with the AgNPs-citrate surface and cause surface neutralization. It can decrease the particles' distance and discoloration of the surface resonance properties of the nanoparticle plasmon. Consequently, the plasmon absorption band will be reduced by the appearance of a new absorption band at a larger wavelength.

Surface Modification of AgNPs by Adding Organic Acids

Modification with organic acids can be used as an effort to increase the stability of AgNPs. The stability of AgNp without modification studied by Badi'ah et al. [48] results in the bathochromic shift. The absorbance value increases with increasing time until the maximum absorbance value is reached within 12 h, and after that, the absorbance begins to decrease, and finally, the peak widens [48]. Organic acids such as ascorbic acid [41], chromotropic acid [15], *p*-coumaric acid [49], and folic acid [50] can be as reducing agents as well as stabilizers by covering the surface of AgNPs, thereby reducing the occurrence of particle aggregation. Apart from being a reducing agent, folic acid is capable of being a molecular template. So it can detect target molecules selectively. The selection of organic acids must pay attention to their functional groups because functional groups such as carbonyl, hydroxy, and hydroxy phenols in *p*-coumaric acid can potentially interact with AgNPs and analytes. Folic acid has carboxylic acid groups and amine groups that can coordinate Ag ions with good geometry, whereby involving the reduction of Ag^+ ions to Ag^0, molecular networks will be formed on the surface of AgNPs. A modified organic acid-binding scheme has been studied by D'souza et al. [41], who modified the surface of AgNPs with ascorbic acid that uses for the detection of glutathione in an aqueous solution. This detection mechanism is based on an induced aggregation of ascorbic acid-AgNPs and results in the drastic changes in the color confirmed by UV-Vis spectrophotometry with various ascorbic acid concentrations [41].

Surface Modification with Organic Ligands

It can increase the stability of AgNPs because the amine, thiol, carbonyl, and carboxylic acid functional groups belong to an organic compound. These compounds can be used as AgNPs stabilizer candidates, such as polymer chitosan [2,8]. Chitosan was chosen as a capping agent because chitosan can function as a modifier that causes polymer adsorption on the surface of nanoparticles, thereby creating steric stabilization. Steric stabilization occurs due to the interaction of the amine group in chitosan with Ag metal. The nitrogen in chitosan acts as a Lewis base that donates its electron pair to the empty Ag orbital to form an Ag–N bond. The interaction of the analyte with chitosan is predicted by hydrogen bonding and electrostatic interactions. So, with the presence of analytes, AgNPs-Chitosan aggregation is induced and results in visible color changes as Badi'ah [51] used it for colorimetric detection of sialic acid. Other compounds, for example, are dopamine [10-11]. Dopamine has free –OH and $–NH_2$ groups and shows a high potential to react with thiols and amines via Michael addition reactions or enamine formation. This dopamine dithiocarbamate (DDTC) derivative is prepared by reacting dopamine with CS_2. DDTC is of particular interest in nanotechnology applications because of its chemical supramolecular on the surface of the nanoparticles. Other compounds that can act as organic ligands are L-cysteine [14], melamine [9], polyvinyl pyrrolidine [17,52], and biothiols [6].

Surface Modification with Other Compounds

Other compounds that can be chosen are arene compounds [12,40,42,45], surfactants [4], crown compounds [53], complex compounds [23], and silica

[18]. Many of these compounds have been reported to increase the stability of AgNPs through their interaction with Ag metal. The aza-crown ether compound can modify AgNPs and form Ag-S bonds [53].

pH

pH optimization is one of the most important factors in the manufacture of AgNPs-based colorimetric sensors. Because it is related to the functional groups between the analytes and AgNPs and their stabilizers. Besides, knowledge of the pKa of AgNPs analytes or stabilizers should also be considered for selecting the pH sensor test range. This is related to the protonation/ deprotonation process of functional groups, which can affect the electrostatic interaction of the analyte with the sensor, which causes a decrease in absorbance or the absence of new absorption bands after the addition of the analyte, which indicates that the sensor is not working properly.

In practice, pH optimization can be done by adding a solution of Tris HCl buffer, phosphate buffer, acetate buffer, NaOH, HCl, and citrate buffer. The optimum pH can be determined with UV-Vis spectrophotometry by looking at the absorption band and the maximum absorbance. Table 1 summarizes the pH optimization of several AgNPs-based colorimetric sensors for detecting a wide variety of analytes.

D'souza et al. [41] research, optimization of pH has been carried out to investigate the effect of pH condition on colorimetry sensor of AA-AgNPs that use for glutathione detection in aqueous samples. Based on the result, at the lower pH (2.0–4.0), the UV-Vis spectra of AA-AgNPs are drastically changed due to the surface neutralization of AA-AgNPs. At pH 7.0, the color and absorption spectrum of AA-AgNPs did not influence sodium acetate buffer pH [41].

Inamuddin and Kanchi [54] have done research about colorimetric sensing based on a silver nanoparticle that was used to detect melamine in biological samples. The optimization of pH was studied with the range from 1.0–14.0 using 5 ppm of melamine. The maximum absorption was observed at pH 7.0 and decreased from pH 7.0–14.0 [54].

Temperature

Several studies have reported that temperature is a key factor affecting the stability of AgNPs and the reaction rate. Optimization at various temperatures is carried out to get the best results. As in the research of Kappi et al. [9], which tested the effect of temperature from 0–60 °C on the MA-AgNPs sensor in the detection of cyanuric acid (CYA). The results show that the signal decreases with increasing temperature. This illustrates the decrease in sensor stability. Therefore, the solution was incubated at 5 °C.

Table 1. List of pH optimizations on colorimetric sensors based on AgNPs

Sensor	Analyte	pH test range	pH optimum	Ref.
DDTC-AgNPs	Mancozeb	2.0–11.0	9	[11]
AgNPs	Etimicin	3.29–10.38	5.72	[3]
AgNPs-citrate	Ampicillin	2–9	4	[1]
AA-AgNPs	GSH (glutathione)	2–10	7	[41]
Chitosan-AgNPs	Biothiols	-	8	[2]
AgNP-Chitosan	Sialic acid	3–8	6	[8]
CA-AgNPs	Melamine	3–8	7	[16]
AgNP-Tyr	Cysteine	6–10	7.4	[6]
cc-AgNP	Creatinine	-	12	[5]
MA-AgNPs	Cyanuric acid	6.5–8.0	7	[9]
PVP-AgNPs	Arginine	5–9	9	[52]
CTA-AgNPs	Melamine	-	9.2	[15]
AgNPs-citrate	GABA	3.8, 4.6, 5.6	3.8	[19]
AgNPs-citrate	Azitomicin	3–6.7	4.4	[7]
FA-AgNPs	6-mercaptopurine	2–12	7	[50]

Temperature can also affect the electrostatic attraction and hydrogen bonds between AgNPs and analytes, such as in Li et al.'s study [3] on detecting etimicin. In this case, the absorbance ratio decreases when the temperature is below 18 °C and maximum at 18 °C. This indicates that the movement of AgNPs and etimicin is getting faster with increasing temperature, making it difficult to interact. However, the reaction is slow at low temperatures. Therefore, the room temperature was chosen for experimentation.

Fu et al. [55], that use silver nanoparticles as a colorimetric sensor for mercury detection in the environment, also evaluated several factors optimization on the formation of AgNPs, including reaction temperature. The formation reaction of silver nanoparticles was compared with the use of hot water and an ice bath. When using hot water, the characteristic of the color and absorption is better than in cold water [55].

Concentration of Precursors

The concentration of precursors in the synthesis of AgNPs, such as the concentration of $AgNO_3$, the reducing agent, as well as the stabilizer, is of concern. Because it is related to the perfection of the AgNPs formation reaction, it has been widely reported that in the synthesis of AgNPs, the concentration of $NaBH_4$ must be higher than $AgNO_3$, as in the study of Mulfinger et al. [46], which reported that the concentration ratio between $NaBH_4$ and $AgNO_3$ was 2 so that if the concentration of $AgNO_3$ was 1.0 mM, the concentration of $NaBH_4$ was added by 2.0 mM. This is related to the ability to reduce $NaBH_4$ against Ag^+ ions, where a large concentration of $NaBH_4$ can reduce more Ag^+ ions to Ag^0 so that the redox reaction will continue for the specified reaction time and prevent particle aggregation, which causes the particle size of AgNPs to become larger [16]. Meanwhile, if the concentration of $AgNO_3$ is greater than $NaBH_4$, it will cause the reduction reaction to run very fast, so it will accelerate the particle aggregation. Besides, the number of Ag^+ ions is more, so the amount of $NaBH_4$ as a reducing agent and stabilizer needs to be added.

Determination of the optimum concentration was characterized by UV-Vis spectrophotometry and PSA (Particle Size Analyzer). The optimum result shows the maximum absorbance, which indicates the formation of more AgNPs. Besides, it can also be observed from the FWHM value, which shows the homogeneity of the nanoparticle size. If the FWHM value of a solution is small, the homogeneity of the particle size will be greater [8]. The particle size resulting from the synthesis of each concentration was confirmed by PSA.

Besides, the concentration of AgNPs stabilizer needs to be considered because it is related to the number of functional groups present on the AgNPs surface that interact with the analyte [2] and which play a role in maintaining AgNPs in a stable dispersion phase [15]. If the composition or ratio of the stabilizer to Ag is not suitable, the stabilizer does not completely modify the AgNPs [2,8,15]. Besides, it is also necessary to pay attention to whether the stabilizer can react directly with the analyte, which causes a reaction competition between the stabilizer-analyte and AgNPs-stabilizer-analyte because the excess of the stabilizer will stimulate the aggregation of AgNPs to increase the absorbance of the blank [9] or create clusters between stabilizers, for example, chitosan-chitosan [8].

The effect of $AgNO_3$ concentration was evaluated by Badi'ah et al. [48], that used AgNPs as a colorimetric sensor for the detection of melamine in an aqueous solution and sialic acid in a serum sample. The result of the maximum concentration of $AgNO_3$ is 1.0 mM with an absorbance of 0.345, and this concentration results in a size distribution are 34.06 nm [48].

Reaction Time

The reaction time was tested to determine the optimum time for the analyte to aggregate perfectly with AgNPs. Besides, the reaction time shows how effectively and efficiently the sensor detects the analyte. The sooner it is detected, the better the sensor quality. The reaction time is observed by looking at the absorbance of the solution over a certain time. The optimum reaction time is shown from the largest or maximum absorbance value, which indicates that the analyte is sufficiently aggregated with AgNPs [54,56]. The optimum detection time can be illustrated by the following graph from the

interaction between AgNPs and melamine [54], where there will be an increase in absorbance at the beginning of time until it reaches the maximum time and experiences a decrease or absorbance stability or does not experience a significant change.

Salt Addition

The effect of ionic strength is usually studied through salt addition such as NaCl [4,14,17] and $NaNO_3$ [2]. The addition of salt in several studies affected the aggregation rate of AgNPs in the presence of analytes. As in the research of Chen et al. [4], with the capping agent fluorosurfactant anionic compound wherein low salt concentrations, AgNPs-fluorosurfactant aggregation may be impeded by electrostatic repulsion between particles so that the aggregation rate slows down. Whereas at high NaCl concentrations (70 mM), the electrostatic interactions can be quickly filtered out effectively, the London - Van der Waals attractions play a major role in particle aggregation through the crosslinking mechanism. The prepared AgNPs can withstand the effects of salts effectively, and only very high ionic strengths can significantly impact the stability of the AgNPs [17]. Meanwhile, in other analytes, such as detection of biothiols with AgNPs-chitosan [2], detection of arginine with PVP-AgNPs [52] did not show a significant response, meaning that there was no effect of adding salt to the sensor signal.

The addition of salt usually serves to regulate ionic strength, resulting in a rapid color change in colorimetric reactions. As in the research of Nafia [14], NaCl salt makes AgNPs-L-cysteine experience a rapid color change from brown to yellow, which is indicated by a decrease in the absorbance spectrum of UV-Vis. Besides, NaCl is added during the analysis process to maintain the stability of the nanoparticles.

■ SELECTIVITY TEST OF SENSOR

Selectivity or specificity is the ability of a method to determine the analyte accurately and specifically in the presence of other compounds that may be present in the sample matrix under the optimum conditions of analysis [57-59]. Selectivity is often performed by comparing the results of the analysis of a sample containing a confounding compound with a sample without a distraction or by comparing the results of other methods such as chromatography. The composition of the matrix in chemical and biological samples is almost similar. It's just that in biological samples, it contains a matrix of organic compounds such as amino acids and proteins. Whereas, in chemical samples, the sample matrix is usually inorganic compounds such as heavy metals.

Biological samples such as urine and blood plasma are often tested to detect disease-causing analytes or what are known as biomarkers, amino acids, and medicinal compounds that are excreted in the urine. However, there are many analytes tested that test for metal ions in urine samples. Like the research of Shrivas et al. [1] to test the drug ampicillin, selectivity tests were carried out for nicotine amide, nicotinic acid, urea, cysteine, isoleucine, alanine, Na^+, K^+, Ca^{2+}, Cl^-, PO_4^{3-}, uric acid, bilirubin, creatinine, and glucose which may be in the urine sample. The test was carried out by adding each solution into a separate glass containing AgNPs at pH 4. The mixture was stored for 5 min. The results showed that the presence of the matrix did not interfere with the analysis process. This means that the sensor is designed to have good selectivity to the analyte. Table 2 shows the selectivity tests of various analytes in chemical and biological samples.

■ COLORIMETRIC SENSOR SENSITIVITY

The sensitivity of a colorimetric method is the gradient of the sensor response curve. In practice, sensitivity leads to the slope of the calibration curve. Usually discussed together with Limit of detection (LOD) and Limit of Quantitation (LOQs). LOD is the smallest amount or concentration of analyte that can still be measured or detected with statistical reasons confidence. LOQs are the smallest amount or concentration of analytes that can be determined quantitatively with the acceptability of repeatability, precision, and confidence. Table 3 summarizes some of the measurement detection limits resulting from the development of an AgNPs-based colorimetric sensor. A method is said to be sensitive if the smallest change in the concentration or amount of analyte might cause a large change in the measurement signal [57].

Table 2. Selectivity test on various samples

Sensor	Analyte	Sample	Selectivity	Results	Ref.
AgNPs	Ampicillin	Urine	Nicotine amide, nicotinic acid, urea, cysteine, isoleucine, alanine, Na^+, K^+, Ca^{2+}, Cl^-, PO_4^{3-}, uric acid, bilirubin, creatinine, and glucose	Selective to ampicillin	[1]
cc-AgNPs	Creatinine	Urine	Ca^{2+}, K^+, Fe^{2+}, Fe^{3+}, Na^+, Zn^{2+}, ascorbic acid, glucose, glutamic acid, urea, glycine, uric acid	Selective to creatinine	[5]
Chitosan-AgNPs	Biothiols (Cysteine, glutathione, homocysteine)	Urine and blood plasma	Alanine, arginine, asparagine, aspartic acid, glutamine, glycine, histidine, leucine, methionine, phenylalanine, proline, serine, threonine, tryptophan, tyrosine, valine, and then urea and glucose	Selective to biothiols	[2]
FA-AgNPs	6-MP	Urine and blood plasma	Na^+, K^+, Cu^{2+}, Fe^{2+}, Mn^{2+}, Mg^{2+}, Co^{2+}, Pb^{2+}, Ca^{2+}, Cr^{3+}, Fe^{3+}, Al^{3+}, Cl^-, I^-, Br^-, NO^{3-}, SO_4^{2-}, $Cr_2O_7^{2-}$, ATP, AMP, BSA, GSH, isatine, guanosine, guanine, thymine, urea, uric acid, glucose, uracil, chloramphenicol, fluorouracil, flutamide, neomycin, kanamycin, vancomycin, and amoxicillin	Selective to analyte 6-MP	[50]
AgNPs	Etimicin	Urine	Glucose, lactose, amino acid (Try, Thr, Ser, and Ala), ion Na^+, K^+, Ca^{2+}, NH_4^+, Cl^-, SO_4^{2-}, PO_4^{3-} and urea	Selective to etimicin	[3]
AgNPs-Chitosan	Sialic acid	Blood serum	glucose, galactose, ascorbic acid, uric acid	Good selectivity to sialic acid	[8]
CTA-AgNPs	Melamine	Milk	*1-fold* Lys, Arg, and His; *20-folds* Mg^{2+}, Ca^{2+}; *50-folds* Gly, Ala, Phe, D-galactose, D-fructose, L-arabinose, D-mannose, D-glucose, and sucrose; and *200-folds* EDTA, Mg^{2+}, Ca^{2+}, Zn^{2+}, Fe^{3+}, Na^+, K^+, and amino acids such as Lys, Arg, and His	Mg^{2+}, Ca^{2+}, Zn^{2+}, Fe^{3+}, Na^+, K^+ don't interfere with the existence of EDTA; Lys, Arg, and His can interact with CTA through hydrogen bonds. But can be avoided by removing protein in milk	[15]
Cit-AgNPs	Melamine & H_2O_2	Milk and rainwater	vitamin C, tyrosine, alanine, tryptophan, methionine, glucose, glycerol, urea, $CaCl_2$, $FeCl_3$, KCl, $MgCl_2$, $ZnSO_4$, KBr, $MnSO_4$	Selective to analyte	[13]
DDTC-AgNPs	Mancozeb	Water and fruit juice	Several kinds of pesticides (thirum, acephate, quinalphos, clodinofop, sulphosulphuran, ion Mn^{2+}, and Zn^{2+}), isoproturon, sulfosulfuron, carbendazim, acephate, monocrotophos, metsulphuron, imidacloprid, clopropham, glyphosate	Selective to mancozeb	[11]
CA-AgNPs	Melamine	Milk	Na^+, Ca^{2+}, K^+, Mg^{2+}, galactose, glucose	Selective to melamine	[16]
DA-AgNPs	Ascorbic acid	Tablet and lemonade drink	glucose (Glu), alanine (Ala), urea, oxalic acid, citric acid, Na_2CO_3, $Mg(NO_3)_2$, NaCl, $ZnSO_4$, $Ca(NO_3)_2$, $NaNO_3$ and KNO_3	Selective to ascorbic acid	[22]
AgNPs	Timolol	drugs	Ca^{2+}, Cu^{2+}, Fe^{3+}, K^+, Mg^{2+}, Mn^{2+}, Na^+, Ni^{2+} and Zn^{2+}, L-ascorbic acid and malic acid	Selective to timolol	[17]
cc-AgNPs	4 family of triptan drugs	drugs and *nasal spray*	Amoxicillin, ampicillin, cortisone, cyclosporine, methylcobalamin, tramadol	Good selectivity	[21]
cc-AgNPs	γ-aminobutyric acid (GABA)	Pharmaceutical drugs	Na^+, K^+ and Mg^{2+}, glucose, fructose, glycine, and vitamin B6	Selective to GABA	[19]
cc-AgNPs	AZT	Human plasma and pharmaceutical drugs	erythromycin, clarithromycin, roxithromycin and doxycycline, Na^+, K^+, NH_4^+, Mg^{2+}, Ca^{2+}, Fe^{3+}, and anion Cl^-, NO_3^- and SO_4^{2-}	There is no effect until the concentration is 50x higher than AZT	[7]
ZnLATP-AgNPs	Arginine	Supplement tablet	Ala, Asn, Asp, Cys, Gln, Glu, His, Ile, Leu, Lys, Met, Phe, Pro, Ser, Thr, Trp, Val	Good selectivity	[23]
Dopamin/AgNPs	Cu^{2+}	Tap water	Li^+, Na^+, K^+, Mg^{2+}, Ca^{2+}, Sr^{2+}, Zn^{2+}, Co^{2+}, Ni^{2+}, Ba^{2+}, Cr^{6+}, Al^{3+}, Fe^{2+}, Fe^{3+}, Pb^{2+}, Hg^{2+} and Cd^{2+}	The addition of sodium oxalate can solve disturbances of Fe^{2+}, Fe^{3+}, and Pb^{2+} but failed to prevent Hg^{2+} and Cd^{2+} disorders.	[10]

Sensor	Analyte	Sample	Selectivity	Results	Ref.
PVP-AgNPs	Arginine	Sample of water media	Phenylalanine, tryptophan, tyrosine, methionine, alanine, and arginine	Selective to arginine	[52]
1,3-1lternat calix[4]arene – AgNPs	Cu^{2+}	Water	Ni^{2+}, Zn^{2+}, Co^{2+}, Mn^{2+}, Ag^{+}, Hg^{2+}, Pb^{2+}, Cd^{2+}, Ba^{2+}	Selective to Cu^{2+}	[42]
ACE-AgNPs	Ba^{2+}	Water	Li^{+}, Na^{+}, K^{+}, Cs^{+}, Mg^{2+}, Ca^{2+}, Ba^{2+} and Sr^{2+}	Selective to Ba^{2+}	[53]
AA-AgNPs	GSH	Biological sample	Threonine, histidine, glutamic acid, serine, lycine HCl, cysteine, tyrosine, and tryptophan	High selectivity to GSH	[41]
MA-AgNPs	CYA	Water	Al^{3+}, Cu^{2+}, Fe^{3+}, Ni_2^{+} and Co^{2+}, Na^{+}, K^{+}, NH_4^{+}, PO_4^{3-}, Cl^{-}, SO_4^{2-}, NO_3^{-}, chlorine, urea, and humic substances	Selective to CYA	[9]
pSC_6-AgNPs	$H_2PO_4^{-}$	Water	F^{-}, Cl^{-}, Br^{-}, I^{-}, HSO_3^{-}, SO_4^{2-}, NO_3^{-}, NO_2^{-}, HCO_3^{-}	Good selectivity	[45]

Table 3. Detection limits of several developments in the AgNPs colorimetric sensor methods

Sensor	Analyte	Linearity range	LOD	Ref.
cc- AgNPs	Creatinine	0.0–4.2 µM	53.4 nM	[5]
AgNPs	Timolol	10^{-7}–10^{-3} M	1.2×10^{-6} M	[17]
AgNPs-Chitosan	Sialic acid	0.007–0.57 mM	0.009 mM	[8]
PVP - AgNPs	Arginine	200–700 nm	0.1 nM	[52]
AgNPs	AZT	0.2–100.0 M	Up to 200 µM	[7]
Nonionic fluorosurfactant AgNPs	Cysteine	1.5–6.0 µM	0.05 µM	[4]
AA- AgNPs	GSH	5–50 µM	2.4×10^{-7} µM	[41]
AgNPs	H_2O_2 and TATP	TATP: 1.25-31.25 mg/L H_2O_2: 2.5×10^{-6}–4×10^{-5} M	H_2O_2 20 nM TATP 0.31 mg/L	[64]
pSC6 – dipirene AgNPs	$H_2PO_4^{-}$	10^{-2}–10^{-8} M	10^{-7} M	[45]
cc-AgNPs	Gamma-aminobutyric acid (GABA)	100–500 mg/L	57.7 mg/L	[19]
MA- AgNPs	Cyanuric acid	1.0–6.5 mg/L	0.6 mg/L (blank) 0.25 mg/L 3× SD blank	[9]
Citric-AgNPs	4 family triptan drugs	0.001–1.0 mM	Rizatripan: 7.3 nM Naratripan: 8.6 nM Sumatripan: 10.5 nM Zolmitripan: 84.0 nM	[21]
ACE-AgNPs	Ba^{2+}	10^{-3}–10^{-8} M	10^{-8} M	[53]
AgNPs	Etimicine	3.25×10^{-7}–6.75×10^{-7} mol/L	3.59×10^{-7} mol/L	[3]
AgNPs	Dopamine	0.0–0.06 µM	60 nM	[65]
AgNPs/dopamine	Cu^{2+}	3.2–512 ppb	0.03 µM	[10]
AgNPs-chitosan	Biothiols	0.1–10.0 µM	Cysteine: 15.0 nM Homocysteine: 84.6 nM Glutathione: 40.0 nM	[2]
1,3-alternate calix[4[arene - AgNPs	Cu^{2+}	-	LOQ 2.5×10^{-6} M LOD 1×10^{-6} M	[42]
FA-AgNPs	6-MP	20–1000 nM	13.2 nM	[50]
DDTC-AgNPs	Mancozeb a member of the ethylene-bis (dithiocarbamate) EEDC	5×10^{-5}–3×10^{-4} M	21.1×10^{-6} M	[11]

Sensor	Analyte	Linearity range	LOD	Ref.
AgNPs	Ascorbic acid	0.25–25 μM	0.054 μM	[22]
CA-AgNPs	Melamine	0.1–4 μM	0.05 μM	[16]
Citric -AgNPs	Ampiciline	25–1200 ng/L	10 ng/l	[1]
CTA- AgNPs	Melamine	0.1–1.5 μM	36 nM	[15]
AgNP- tyr	Biothiols (glutathione dan Cysteamine)	10×10^{-6}–5×10^{-8} M (Cysteamine) 1×10^{-5}–5×10^{-7} M (GSH)	Cysteamine: 1.80×10^{-8} M GSH: 3.68×10^{-7} M	[6]
ZnLATP- AgNPs	Arginine	0.1–4.0 μM and 4–12 μM	LOQ 200 ± 15 nM LOD 2 μM	[23]
Cit-AgNPs	Melamine & H_2O_2	MA 0.2 nM–3 μM H_2O_2 0.6 nM–5 μM	H_2O_2 0.2 nM MA 0.08 nM	[13]
pSC4- AgNPs and pSC8-AgNPs	Pesticides	5×10^{-6}–10^{-3} M	10^{-7} M	[12]
Pyridyl-appended fluorescent calix[4]arene – AgNPs	Fe^{3+}	2.5×10^{-6}–$1.5\ 10^{-4}$ M	125 μM	[66]
Electrochemically-AgNPs (e-AgNPs)	Acrylamide	0.1–1000 μM	0.024 μM	[67]
Fluorescein-AgNPs (F-AgNPs)	Tricyclazole	0.006–1.0 ppm	0.051 ppm	[68]
AgNPs	Zn (II)	0.2–2.0 mM	0.2 mM	[69]
Sodium gluconate-AgNPs (GA-AgNPs)	Creatinine	0.3–50 nM	0.2 nM	[70]

■ CHARACTERIZATION OF THE AgNPs SENSOR

Maximum Wavelength and Absorbance

The synthesized AgNPs can be confirmed by UV-Vis spectrophotometry which is shown by a maximum wavelength of about 400 nm. The stable AgNPs are characterized by the formation of yellow, silver colloids. Measurements with a UV-Vis spectrophotometry associated with the metal nanoparticle LSPR. Where the LSPR excitation is induced by the electric field of the incident rays where resonance occurs, the displacement of the electron cloud due to the electric field makes the surface positively charged when it loses electrons and negatively charged when it has excess electrons. When resonance occurs, a strong absorption band emerges from the surface of the plasmon. The position, shape, and intensity of the LSPR are a function of several factors, such as the shape, size, composition of the particles, the distance between the particles and the adsorbed species, and the dielectric constant of the medium.

The LSPR of plasmonic nanoparticles change can present analytes in two ways [60]: (1) the appearance of a new peak as a result of nanoparticles aggregation in the presence of the analyte; (2) the decrease or increase in peak intensity from the interaction of AgNPs and analyte. The aggregation mechanism between AgNPs and analytes causes the color to change from yellow to red-purplish. This aggregate also can cause the appearance new peak at 563 nm, which is thought to be the peak of a new complex formed by the bond between AgNPs and analytes [48]. In addition, the aggregation causes the decrease or increase or with or without the appearance of a new peak that is proportional to the analyte concentration [60]. From the study of Laliwala et al. [21], it is stated that based on UV-Vis spectrophotometry data, an estimate of the diameter of a particle can be determined using the Mie Scattering theory approach.

$$\omega = \frac{\left(\varepsilon_0 + 2n^2\right) cm\mu_F}{2N_c e^2 D} \quad (2)$$

where ω is Full Width at Half Maxima (FWHM) of the signal peak following Lorentz form, ε_0 is dielectric constant, n is the solvent refractive index of water, c is

fast propagation of light, m is the mass of the electron, μ_F is electron velocity in Fermi energy, N_c is some electrons per unit volume, e is the electron charge, and D is Particle diameter. For example, if known $\omega = 22.34$, $\varepsilon_0 = 4.9$, $n = 1.33$, $\mu_F = 1.4 \times 106$, $N_c e^2/m = 1.7 \times 10^{31}$, then by entering into the above equation it can be obtained D of 4.66 nm [21].

Prediction of Functional Groups and Bonds

Prediction of functional groups and bonds can be characterized by FTIR. FTIR is one of the infrared spectroscopic methods equipped with Fourier transformative to analyze the spectrum results. The method in this instrument is absorption which is based on the different absorption of infrared radiation. A material can absorb the infrared if the frequency of infrared radiation matches the vibrational frequency of the sample molecules as well as the change in dipole moments during vibrations. In various studies, there will be differences in spectra between AgNPs-stabilizers and AgNPs-stabilizers-analytes. The difference in spectra of stabilizing compounds such as ascorbic acid and the results of its modification with AgNPs can be seen that the hydroxy group on ascorbic acid, which appears as OH-stretching at a wave number around 3500, is not reabsorbed after interacting with AgNPs. So it can be predicted that Ag-O bonds are formed in AA-AgNPs [61].

From the study of Badi'ah [51], the success of stabilization AgNPs and chitosan can confirm by FTIR. The FTIR peak between chitosan and AgNPs-chitosan had an absorption band of –OH groups in 3427.62 and 3448.84 cm^{-1}, respectively. The CO group in chitosan had an absorption in the 1072.46 and 1053.17 cm^{-1} when AgNPS stabilized with chitosan. –NH group of chitosan resulted in the band in an area of 1575.89 cm^{-1} and lost the absorption after stabilization AgNPs with chitosan [51].

Distribution, Size Estimation, and Surface Morphology of Particles

Transmission electron microscopy (TEM)

The working principle of TEM, in brief, is the electron beam illuminates the specimen and produces an image on the phosphor screen. This characterization shows the morphology and size of the nanoparticles with a partial degree of aggregation and variation in the particle size range.

The characterization with TEM result shows that the particle's size range from 15 to 85 nm. AgNPs synthesized with borohydride has a stable shape and size for up to one year. AgNP synthesized using lactose result the shape of the particle was spherical with an average of 20 ± 5 nm with a low degree of aggregation. TEM image of AgNPs synthesized by the citrate method, resulting in a spherical particle shape with an average size range from 7 to 11 nm [62].

Dynamic light scattering (DLS)

Dynamic Light Scattering (DLS) is based on the Brownian motion of dispersed particles. When the particles are dispersed in the liquid, they move randomly in all directions. The Brownian principle of motion is that particles constantly collide with solvent molecules. This collision causes a certain amount of energy to be transferred, which induces the movement of the particles. The energy transfer is more or less constant, so it has a greater effect on the smaller particles. As a result, smaller particles move at a higher speed than larger particles. The relationship between particle velocity and particle size is given by the following Stokes-Einstein equation:

$$D = \frac{k_B T}{6\pi\eta R_H} \quad (3)$$

where D is diffusion translation coefficient/particle velocity (m^2/s), k_B is Boltzmann constant ($m^2kg/K.s^2$), T is temperature (K), η is viscosity (Pa.s) and R_H is hydrodynamic radius (m). The particle velocity is given by the translational diffusion coefficient D. The equation includes the viscosity of the dispersion and temperature because these two parameters directly affect the motion of the particles. The basic requirement for the Stokes-Einstein equation is that the motion of particles must be based solely on Brownian motion. If there is sedimentation, there is no random movement, which will lead to inaccurate results. Hence, the incidence of sedimentation represents an upper size limit for DLS measurements. Conversely, the lower size limit is determined by the signal-to-noise ratio.

Characterization using DLS is usually carried out before and after AgNPs are given the analyte. Then the

histogram results will be compared. The size of the AgNPs will increase when they interact with the analyte or have undergone aggregation. This proves that the analyte-induced aggregation through various interactions such as covalence, coordination, π–π, and charge transfer [11]. From the research of Erjaee et al. [63], the particle size measurement using DLS results in the mean size of AgNPs at optimum conditions is 46.3 nm, and the range of nanoparticles was from 39 to 78.5 nm.

■ COLORIMETRIC SENSOR BASED ON AgNPs

In the colorimetric test, two important factors play a role in increasing the selectivity and sensitivity of metal nanoparticle-based colorimetric sensors. The first is the ability to recognize metal nanoparticle probes to target molecules/analytes through specific interactions. The second is the conversion of the measured signal from the sample into the optical response, thereby causing a change in spectra with color intensity in the visual region (390–750 nm) [20]. Colorimetry is a good method of analyte detection, simple, fast, and observable only with the naked eye [13]. This is due to the excellent adsorption of plasmon from precious metal nanoparticles, especially gold and silver. The following will discuss an example of the development of AgNPs-based colorimetry in detecting various types of analytes with good sensitivity and selectivity.

Melamine is a pollutant in milk that has been detected by this method. for examples chromotropic acid-modified AgNps (CTA-AgNPs) [15], cysteamine (CA-AgNPs) [16], and *p*-coumaric acid (APK-AgNPs) [49]. This test is also characterized by a greater shift in wavelength. CA-AgNp, APK-AgNPs, and CTA-AgNPs are visually yellow (395–400 nm), while the presence of melamine causes a burgundy or brownish color change with new peaks appearing in the 530–560 nm wavelength range. This sensor was characterized using FTIR, UV-Vis spectrophotometry, XRD (X-Ray Diffraction), TEM, and PSA. In the presence of melamine, aggregation occurs more rapidly, as shown by the CA-AgNPs sensor only takes 3 min to change color [16].

Besides being detectable, melamine can also be used as a stabilizer for AgNPs (MA-AgNPs) for the determination of cyanuric acid (CYA) [9]. The principle of detection of cyanuric acid is based on two complementary reactions. The first is the self-assembly of a molecule from CYA through the three hydrogen bonds NH---O and NH---N, which complement each other between the enol form melamine and the keto cyanurate form. The second is the coordination of melamine with the AgNPs surface via its exocyclic amino groups, replacing surface-bound stabilizing anions and promoting aggregation. The LSPR shift is demonstrated by adding melamine directly to the sample to form the melamine-CYA complex via hydrogen bonding and then adding the AgNPs. UV-Vis results show a new absorption peak at 525 nm by visualizing the solution from green (blank) to purple or reddish-orange at neutral pH (7) because melamine undergoes hydrolysis at acidic and alkaline pH and destabilizes the AgNps suspension. Temperature is also the key to sensor development due to AgNps stability and reaction rate. At high temperatures, the absorption of the signal decreases. This sensor shows good sensitivity, with detection limits of 0.6 and 0.25 mg/L.

■ CONCLUSION AND FUTURE PERSPECTIVE

Analytical methods in chemistry are very interesting to develop. Colorimetry method-based Silver nanoparticles are considered to be the newest method that is simple, affordable, reliable, sensitive, and selective in detecting an analyte. The principle of measurement is based on the color change of the solution, which can be observed with the naked eyes and is the specialty of this sensor. The color change occurs due to the interaction of AgNPs with the analyte, which causes aggregation, so the wavelength is shifted in a larger direction. The molecular interactions and chemical reactions between analytes, AgNPs, and their environment have been creatively designed to increase sensor sensitivity. Electrostatic interactions, hydrogen bonding, and Van der Waals forces have been widely used for the detection of a wide range of molecules such as amino acids, organic molecules, and inorganic ions. With the characterization technique using UV-Vis spectrophotometry, TEM, PSA, FTIR, and DLS, the development of AgNPs-based sensors can be confirmed and evaluated.

According to this review, several strategies have successfully improved the sensitivity and stability, such as a modification of the AgNPs surface. Modification of the AgNPs surface is an important effort to increase the stability by preventing aggregation of the AgNPs surface. Besides, the other parameters such as concentration, pH, reaction time, temperature, selectivity test, and salt addition also need to be considered because they affect sensor performance. Thus, recent efforts have focused on modified AgNPs with controlled size and shape to increase the sensitivity of the resulting colorimetric sensor.

In the future, creativity and innovation based on chemical approaches and insights will continue to be paid attention to in creating good colorimetric sensors of AgNPs. More work in the future will need to be done on the development of AgNPs sensors, including particle size control and attention to sample matrices, to find excellent quantitative results. However, there are some problems with the use of nanoparticles as a routine analysis because of the poor stability of nanoparticles owing to their small size and large surface area, which leads to aggregation. Therefore, the development of the AgNPs-based method is expected to focus topic for years to come. Finally, it is hoped that the development of AgNPs-based colorimetric sensors can use to detect other analytes with more potential in health, industry, environment, and other fields.

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