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Colorimetric Sensor Based on the Interaction of Sildenafil Citrate and Silver Nanoparticles

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ABSTRACT

This study introduces a simple, cost-effective, and highly sensitive colorimetric method for detecting and quantifying Sildenafil Citrate based on the aggregation of citrate-coated silver nanoparticles (AgNPs). The AgNPs were synthesized through the reduction of silver nitrate with sodium borohydride. Under optimized conditions, the presence of Sildenafil Citrate induces a distinct color change in the AgNP solution from light yellow to red, proportional to the Sildenafil Citrate concentration. This aggregation causes a decrease in the localized surface plasmon resonance (LSPR) absorbance at 394 nm and the emergence of a new peak at 530 nm. A linear correlation was established between the Sildenafil Citrate concentration and the absorbance ratio (A530/A394) in the range of 0.34–3.1 µM, with an impressive detection limit of 0.005 µM. The method was successfully applied to quantify Sildenafil Citrate in pharmaceutical tablets, demonstrating high accuracy, excellent stability, and practical applicability for quality control in health products.

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1. Introduction

Recently, the use of colorimetric sensors based on nanomaterials, which can easily detect low concentrations of target analytes with the naked eye, has gained significant attention [1]. Noble metal nanoparticles, which exhibit distinct physical, chemical, and optical properties, have higher extinction coefficients compared to dyes [2]. Moreover, the unique localized surface plasmon resonance (LSPR) properties of nanoparticles, characterized by specific colors, scattering, and aggregation behaviors, make them ideal for sensitive colorimetric detection of various chemical and biological analytes [3]. In brief, LSPR refers to the collective oscillation of conduction electrons in metal nanoparticles when their frequency matches that of incident electromagnetic radiation [4]. The LSPR phenomenon depends on the composition, shape, size, dielectric constant, and the interparticle distance in the surrounding medium [5, 6]. Copper, silver, gold, platinum, and palladium nanoparticles are used for plasmonic applications. It is noteworthy that silver nanoparticles may exhibit toxicity in biological systems, have less chemical stability compared to gold nanoparticles under similar conditions, and can be challenging to use in repeated cycles. However, the use of silver nanoparticles in colorimetry is more common due to their plasmonic band across a wide range of wavelengths (from near-ultraviolet to near-infrared spectra), providing higher sensitivity based on nanoparticle size and shape, improved extinction coefficients, and their cost-effectiveness [7].

In colorimetry, two factors play an important role in increasing selectivity and sensitivity:

1) The ability of the metal nanoparticle sensor to identify target analytes through specific interactions.

2) converting and measuring the signaling information from the sample to the optical response that causes intense spectral changes with intense colors in the visible range [8]. In recent years, the use of colorimetric sensors based on silver and gold nanoparticles has been developed to determine biomolecules [9], metal ions [10], drugs [11], and pesticides [12]. These sensors have disadvantages. For example, auto-aggregation of colloidal nanoparticles leads to false-positive or false-negative results and low selectivity in some studies. However, the lack of simple and economically justified methods that can improve the performance of these sensors is a significant point [1].

Silver nanoparticles are an ideal mineral chromosphere due to their extraordinary photophysical and photochemical properties. For this reason, they are often used in colorimetric systems [13].

The weak point of colorimetric sensors based on silver nanoparticles (AgNPs) is its poor sensitivity, which is caused by the sensitivity to surface oxidation, so surface functionalization plays an important role in increasing the stability and analytical application of silver [14]. In addition, mistakes in the selection of the synthesis method of AgNPs, incorrect optimization of parameters and insufficient knowledge of the matrices in the sample also reduce the sensitivity of the sensor [15].

For the synthesis of silver nanoparticles, there are physical, chemical, photochemical methods, microwave synthesis method, sonochemical method, electrochemical reduction, biological synthesis methods, bacterial synthesis, fungal synthesis, synthesis with plant extract.

Measurement methods based on nanoparticle formation used for the detection and quantification of various analytes involve changes in the plasmonic peak intensity at a specific wavelength and the color intensity of the nanoparticle solution, proportional to the analyte concentration. In these methods, a direct or indirect process reduces metal precursors, forming nanoparticles. Consequently, the nanoparticles' plasmon appears, and its intensity gradually increases. In contrast, in methods based on nanoparticle degradation, the analyte can degrade or oxidize pre-synthesized nanoparticles, leading to a decrease in plasmon peak intensity. Therefore, these methods are used for measuring certain oxidizing compounds, such as nucleic acids [16].

Anti-aggregation measurement methods prevent the aggregation of nanoparticles by an aggregating agent due to the presence of the analyte. The degree of inhibition of aggregation serves as a criterion for analyte quantification. This technique exhibits exceptionally high selectivity due to the specific interaction between the analyte and the aggregating molecule. In the particular case of silver nanoparticles, upon aggregation, the peak around 395 nm (yellow) decreases, and a new peak around 550 nm (red) appears, and the color change of the solution is easily observed [17]. In aggregation-based methods, the analyte induces nanoparticle aggregation by either binding to the nanoparticle surface-stabilizing agent or neutralizing their surface charge. Based on the plasmon peak changes, the intensity ratio of the new peak to the initial peak can be considered as the response and related to the analyte concentration.

Almaquer et al. (2019) employed colorimetry to detect Ni^{2+} in aqueous solutions using citrate-stabilized silver nanoparticles. The interaction of Ni^{2+} with the silver nanoparticles was visually observed by the color change from yellow to orange [18]. Amirjani et al. (2019) developed a colorimetric detection method for determining Hg^{2+} using citrate-functionalized silver nanoplates, synthesized with sodium borohydride reduction, with a wavelength range of 30-40 nanometers. The resulting nanoparticles were fully characterized using UV-Vis spectroscopy, transmission

electron microscopy, energy-dispersive spectroscopy, and X-ray diffraction. The sensor's efficiency was optimized at a pH of 8, considering the interference effect of H^+ ions for Hg^{2+} detection in a basic environment [19].

In the present study, a colorimetric sensor for Sildenafil Citrate was designed based on the interaction between the Sildenafil and citrate-stabilized silver nanoparticles, and its concentration was measured in 100 mg Sildenafil Citrate tablets.

2. Materials and Methods

All the materials were used for synthesis, detection, and measurements in this research work, were obtained from the Merck Company. In addition, Deionized water (Zolal Teb Shimi Company), Sildenafil citrate ($C_{22}H_{30}N_6O_4S$, M = 474.58 g/mol, by Shafa Company) and Sildenafil 100 mg tablet (Amin Pharmaceutical Co.) were other employed chemicals in our study.

The measurements and analysis were performed in UV-Vis Spectrophotometer, Perkin Elmer, model Lambda 35, Transmission Electron Microscope (TEM; model CM120, made in the Netherlands), Dynamic Light Scattering (DLS; model SZ100, Horiba CO.).

2.1. Method of Synthesis of Silver Nanoparticles

In this research, silver nanoparticle solutions were synthesized by reducing silver nitrate using sodium borohydride as a reducing agent and sodium citrate as a stabilizing agent. Briefly, for the synthesis of citrate-stabilized silver nanoparticles at room temperature, 160 µL of a 75 mM silver nitrate solution was added to 100 µL of deionized water under vigorous stirring (800 rpm). After 5 minutes, 160 µL of a 75 mM sodium citrate solution was added. After 15 minutes, 3.84 mL of a cold, fresh 18 mM sodium borohydride solution was added dropwise. Immediately after the addition of the sodium borohydride solution, the color of the solution changed from colorless to pale yellow, confirming the synthesis of silver nanoparticles. After the final drop of sodium borohydride was added, the solution was stirred vigorously for 30 minutes. For extended use, the solution was stored at 4°C in a dark environment [20].

2.2. Recommended procedure for the determination of sildenafil

For preparing different buffers, a 0.1 M solution of acetic acid and citric acid was prepared, and a buffer with pH of 5 was created by gradually adding 0.1 M hydrochloric acid to the solution and using a pH meter to adjust the pH. To prepare the Robinson buffer solution, a mixture of 0.124 gr of boric acid, 139.08 µL of phosphoric acid (85% purity, density of 1.71 g/mL), and 114.38 µL of acetic acid (100% purity, density of 1.05 g/mL) was brought to volume in a 50 mL volumetric flask with deionized water. A buffer with pH of 5 was then prepared by gradually adding 0.1 M hydrochloric acid to the resulting solution and using a pH meter to adjust the pH.

At room temperature, 4 mL of the silver nanoparticle solution and 1 mL of 20 mM sodium chloride solution were transferred to a 10 mL volumetric flask and brought to volume with deionized water. The pH of the solution was adjusted to 5 by adding hydrochloric acid. Then, 100 µL of various concentrations of sildenafil citrate (0.6–5.0 mM) was added to the solution. After 45 minutes, the UV-visible spectrum was recorded using a spectrophotometer, and the magnitude of the absorbance ratio (A575/A408) was carefully recorded.

To measure sildenafil citrate in tablet form, 4 mL of the silver nanoparticle solution and 1 mL of 20 mM sodium chloride solution were transferred to a 10 mL volumetric flask. The pH of the solution was adjusted to 5 by adding hydrochloric acid, and then 100 µL of the actual sample solution was added to the flask. After 45 minutes, the surface plasmon resonance absorption spectrum of the silver nanoparticles in the solution was recorded using a spectrophotometer. This experiment was repeated three times, and the values of A_{530}/A_{394} were calculated. The concentration of Sildenafil was then determined using the calibration curve.

3. Results and Discussion

Figure 1a shows the LSPR absorption spectrum of citrate-coated silver nanoparticles (Cit-Ag). The surface plasmon resonance peak of spherical silver nanoparticles typically appears near 400 nm [21]. The observed maximum absorption at 394 nm confirms the formation of silver nanoparticles. In the presence of sildenafil citrate (SIL), the plasmon absorption spectrum of the silver nanoparticles undergoes a red shift. As seen in Figure 1a, with increasing Sildenafil concentration, the plasmon resonance of the nanoparticles at 394 nm decreases, and a new peak for the silver nanoparticles and sildenafil citrate complex (Cit-Ag-SIL) emerges at 530 nm. Additionally, increasing the Sildenafil concentration results in the aggregation of nanoparticles, leading to a broadening of the plasmon absorption peak. Consequently, the color of the nanoparticle solution changes from yellow to pale purple-gray.

As shown in Figure 2a, the average size of the synthesized silver nanoparticles (Cit-Ag) is 30 nm, and the average size of the nanoparticles in the presence of sildenafil citrate (Cit-Ag-SIL) is 103 nm. According to the DLS results, the size of the synthesized nanoparticles in the absence of sildenafil citrate is significantly smaller than in its presence. Figure 2b shows the measured zeta potential for the synthesized silver nanoparticles (Cit-Ag). The negative zeta

potential indicates that the surface charge of the citrate-coated silver nanoparticles is negative, due to the deprotonation of citrate hydroxyl groups at basic pH, which imparts a negative charge. The zeta potential of the Cit-Ag-SIL complex is -34.6 mV, and upon adding sildenafil citrate, the surface charge of the nanoparticles becomes more negative (-50 mV). This increase in the zeta potential of Cit-Ag upon adding sildenafil citrate further emphasizes the formation of the Ag-SIL complex [22].

Figure 3a shows the TEM image of citrate-coated silver nanoparticles at pH = 5. According to the TEM images, the citrate-coated silver nanoparticles are spherical with a size distribution of approximately 3 nm. In the presence of sildenafil citrate, as shown in Figure 3b, the increase in nanoparticle diameter (with a size distribution of approximately 7.5 nm) is evidence of nanoparticle aggregation.

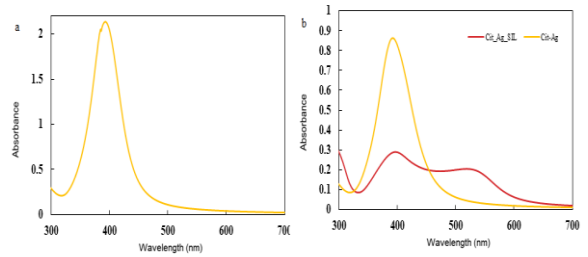

Figure 1: (a) UV-Visible spectrum of citrate-coated silver nanoparticles (Cit-Ag) and (b) Effect of sildenafil citrate presence on the absorption spectrum of Cit-Ag nanoparticles

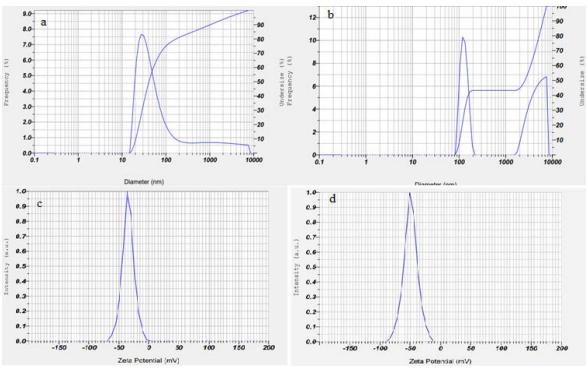

Figure 2: Dynamic light scattering (DLS) analysis for particle size and distribution for citrate-coated silver nanoparticles in the (a) absence of sildenafil citrate; (b) presence of sildenafil citrate; Zeta potential of citrate-coated silver nanoparticles in the (c) absence of sildenafil citrate, and (d) presence of sildenafil citrate.

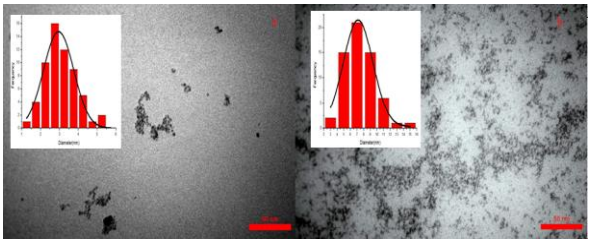

Figure 3: TEM images of citrate-coated silver nanoparticles in the (a) absence of sildenafil citrate and (b) presence of sildenafil citrate

3.1. Investigation of Parameters and Optimization of Variables Affecting the Measurement of Sildenafil Citrate

The presence of functional groups in analytes, silver nanoparticles, and stabilizers plays a crucial role in the fabrication of colorimetric sensors based on nanoparticles. It should be noted that the pK_a of analytes, AgNPs, or stabilizers must also be considered when selecting the pH range for sensor pH investigation, as the protonation/deprotonation process of functional groups can influence the electrostatic interaction between the analyte and the sensor, leading to reduced absorption or the absence of new absorption bands after analyte addition [15].

In order to investigate the effect of pH on the aggregation intensity of silver nanoparticles in the presence of sildenafil citrate, the stability of silver nanoparticles in the absence of the analyte was initially examined within the pH range of 2 to 12. This was monitored using UV-Vis spectroscopy in the wavelength range of 300 to 700 nanometers. The UV-Vis absorption spectrum is presented in Figure 4a.

Considering the pK_a values of the three carboxylic acid groups in citric acid molecules (pK_a values of 3.13, 4.76, and 6.39), at pH < 4, the Cit-Ag solution undergoes aggregation due to the neutralization of negative surface charges on the nanoparticles without the addition of the analyte [5]. At pH 4, although the citrate groups become protonated, the solution remains stable at dilute concentrations; however, the presence of salt leads to nanoparticle aggregation. Despite the absence of new peaks at longer wavelengths, the plasmon peak of the nanoparticles significantly decreases. This reduction could potentially introduce positive errors in the measurement of sildenafil citrate. Figure 4b illustrates the plasmon peak of silver nanoparticles at various pH levels (pH 2 to 8) in the presence of sildenafil citrate.

The sensor response (A_{530}/A_{394}) or, in other words, the extent of nanoparticle aggregation in the presence of 1.36 µmol sildenafil citrate at pH 5 is maximal. Under alkaline conditions, the electrostatic force between molecules decreases due to the deprotonation of citrate groups, leading to a reduction in nanoparticle aggregation. Additionally, the intensity of absorption of the plasmon peak of silver nanoparticles at pH 9 is decreased, which may be attributed to the formation of AgOH precipitates (Figure 4c and d).

The result, the UV-Vis absorption spectrum of Ag-SIL at 1.36 µM sildenafil citrate concentration was studied at pH 5 using different buffer solutions, including acetic acid, citric acid, Robinson, and hydrochloric acid solutions. As observed in Figures 5a to 5d, silver nanoparticles do not aggregate in the presence of Robinson and citric acid buffers, and no new peak or color change was observed. The citrate buffer forms a complex and induces a color change, but

it is not reproducible. The best approach for pH adjustment of the environment is the use of hydrochloric acid.

The measurement of sildenafil citrate by this sensor is based on the aggregation of silver nanoparticles coated with citrate. The ionic strength of the environment plays a determining role in the aggregation process, which may arise from the ability of strong electrolytes to restrict the electrical double layer produced by the stabilizing agent [20]. In the presence of salt, sildenafil citrate penetrates its own charged layers and brings the nanoparticles closer together, leading to their aggregation. The behavior of nanoparticle aggregation at different concentrations of sodium chloride (0-5 mM) in the presence of 1.36 µM sildenafil citrate is illustrated in Figures 6a and 6b. As depicted in Figure 6c, with an increase in salt concentration, the extent of nanoparticle aggregation or, in other words, the sensor response increases. Considering the stability of nanoparticles in the absence of sildenafil citrate, a concentration of 2 mM sodium chloride was selected as the optimal concentration.

The reaction time, or in other words, the time interval between adding sildenafil citrate to the solution and measuring absorption, is a critical parameter in the assay, which must be optimized to enhance sensitivity. The effect of time on the absorption of Cit-Ag was investigated over 80 minutes in the presence of 1.36 µM sildenafil citrate and 40% v/v silver nanoparticles at pH 5, as depicted in Figures 7a and 7b. The absorption intensity ratio (A_{530}/A_{394}) increased gradually over time until particle aggregation reached a steady state after 45 minutes.

Temperature significantly affects the stability of silver nanoparticles and the reaction rate. To achieve the best results, the effect of temperature from 0 to 70 ℃ on the Cit-AgNPs sensor in detecting sildenafil citrate was studied. As illustrated in Figures 7c and 7d, with increasing temperature, the signal decreases, indicating a decrease in sensor stability. Temperature can influence electrostatic attraction and hydrogen bonding between silver nanoparticles and analytes. Additionally, nanoparticle movement accelerates with increasing temperature, making interactions more challenging [5]. Therefore, creating an environment with a low temperature requires temperature control by a circulator. Considering the ease of the provided sensor conditions, it was decided to select room temperature (25°C) as the optimal temperature.

The analytical response of the colorimetric sensor was investigated with different volume percentages of nanoparticles. The aggregation intensities of nanoparticles at various percentages in the presence of 1.36 µM sildenafil citrate and 20 mM sodium chloride were monitored over 45 minutes (Figure 8a and b). Increasing the silver nanoparticles led to an increase in the absorbance signal at 394 nm and enhanced method sensitivity. On the other hand, the increase in absorbance signal at 530 nm, indicating the aggregation of silver nanoparticles due to sildenafil citrate, should also be considered. Therefore, the optimal nanoparticle volume is the one that not only increases absorption at 394 nm but also enhances it at 530 nm. Higher concentrations of silver nanoparticles result in more aggregation in the presence of sildenafil citrate. After reaching 40% volume of silver nanoparticles, a decrease in absorption was observed at 530 nm. Hence, at this stage, 40% was selected as the optimal volume percentage of silver nanoparticles.

To construct a calibration curve, the UV-Vis spectrum of the silver nanoparticle solution was recorded in the presence of various concentrations of sildenafil citrate (Figure 9a) under the optimized conditions determined in this study using 40% volume percentage of silver nanoparticles, 10% sodium chloride at 20 mM concentration, pH of 5, and a reaction time of 45 min. As depicted in Figure 9a, with an increase in sildenafil citrate concentration, the intensity of the plasmon peak of the nanoparticles at the wavelength of 394 nm decreased, while a new peak appeared at 530 nm, accompanied by a color change of the solution from yellow to orange-red (Figure 9c). The absorption ratio plot at 530 nanometers to 394 nanometers (A_{530}/A_{394}) is presented in Figure 9c. The results indicate that the absorption ratio plot at 394 nm to 530 nm is linear in the concentration range of 0.34 to 3.1 µM. The square of the correlation coefficient of the obtained plot (R^2) is 0.9739, indicating a good linear relationship between the values of A_{530}/A_{394} and the drug concentration. The equation of the line is as follows:

$$y = 245010\,C - 0.1053$$

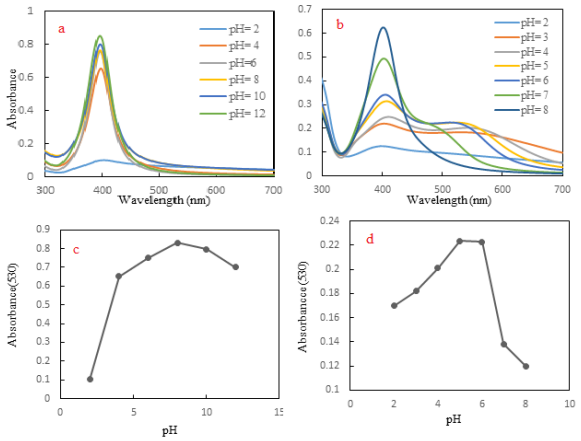

Figure 4: UV-Vis absorption spectra of silver nanoparticles at different pH values in the absence (a) and presence of sildenafil citrate (b), and Changes in the absorption of the plasmon peak of silver nanoparticles at different pH values in the absence (c) and presence of sildenafil citrate (d)

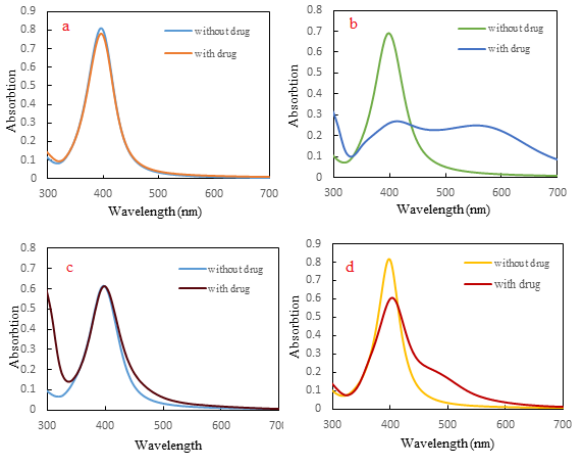

Figure 5: Changes in the absorption of the plasmon peak of silver nanoparticles in Robinson's buffer (a), acetic acid (b), citric acid (c), and hydrochloric acid (d) in the presence and absence of sildenafil citrate

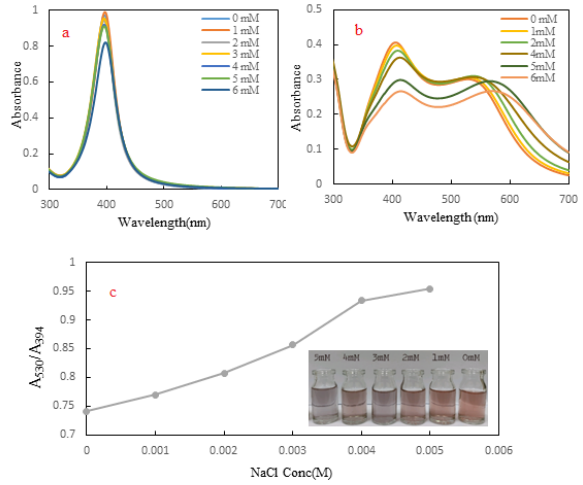

Figure 6: The effect of different salt concentrations on the stability of silver nanoparticles (a) nanoparticle aggregation intensity (b) effect of salt concentration on sensor response (c)

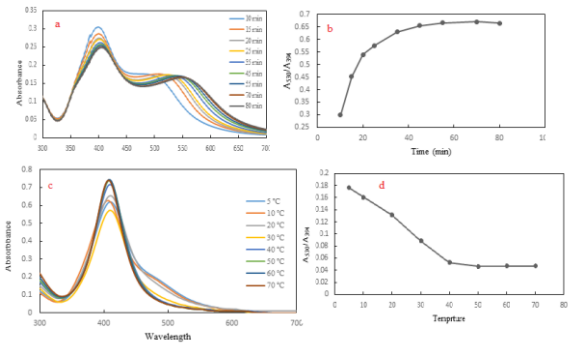

Figure 7: (a) Effect of time on the absorption spectrum of Ag-SIL; (b) Effect of time on sensor response (c); Effect of temperature on the absorption spectrum of Ag-SIL, and (d) Effect of temperature on sensor response

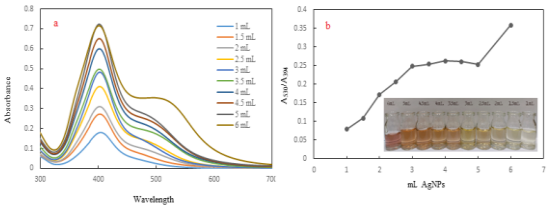

Figure 8: (a) Effect of silver nanoparticle volume on the absorption spectrum of Ag-SIL and (b) Effect of silver nanoparticle volume on sensor response

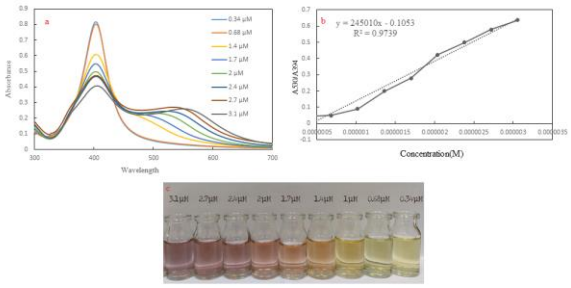

Figure 9: (a) Effect of sildenafil citrate concentration on the absorption spectrum of Ag-SIL; (b) Calibration curve, and (c) Color change of silver nanoparticle solution at different concentrations of sildenafil citrate

3.2. Measurement of Sildenafil Citrate in Real Samples

The experiment was conducted three times to measure Sildenafil Citrate in pharmaceutical tablets and real samples, and the values of *A*530/*A*394 were calculated. Using the calculated *A*530/*A*394 values and the calibration curve, the concentration of the real sample was determined. The calculated concentration and the added concentration were 0.75, 0.78, and 0.79 µM, respectively, resulting in a recovery rate of 101%

3.3. Comparison of the Proposed Method for Sildenafil Citrate Measurement with Reported Methods

Table 1 compares the proposed method in this study with other methods employed by researchers for the measurement of Sildenafil Citrate. As observed in Table 1, this is the first time that Sildenafil Citrate has been examined using a spectrophotometric method, which is simple and does not require complex instrumentation. Although the proposed method has a linear range that is less than other methods, but has a suitable detection limit compared to some other methods. Additional advantages of the proposed method include high sensitivity, accuracy, and repeatability.

To evaluate the selectivity of the proposed method for measuring Sildenafil Citrate, various compounds (metal ions, non-metal ions, and organic compounds) that might be present simultaneously in the measurement environment were examined under optimal conditions. The interference limit of a

compound is defined as the concentration that can change the absorbance by more than 5%. In this case, it is considered an interfering agent. The ions and organic substances, at the reported concentrations and below, listed in Table 2, do not affect the absorbance of a 1.36 µM solution in the presence of other reagents at optimal concentrations, according to the proposed method.

Table 1: Comparison of the Proposed Method with Reported Methods for the Measurement of Sildenafil Citrate

Detection method	Detection limit	Liner range (mol.L^{-})	References
Raman Spectroscopy	4.8×10^{-8}	$1 \times 10^{-7} - 1 \times 10^{-5}$	[22]
Raman Spectroscopy	2.1×10^{-6}	$2.1 \times 10^{-6} - 2.1 \times 10^{-5}$	[23]
Raman Spectroscopy	2.1×10^{-7}	$2.1 \times 10^{-7} - 2.1 \times 10^{-5}$	[24]
Electrochemical Detection	-	$9 \times 10^{-9} - 5 \times 10^{-7}$	[25]
HPLC	3.1×10^{-9}	$1 \times 10^{-8} - 5 \times 10^{-7}$	[26]
LC_MS	2.1×10^{-7}	$2.1 \times 10^{-9} - 2.1 \times 10^{-6}$	[27]
Spectrophotometer	4.898×10^{-9}	$0.34 \times 10^{-6} - 3.1 \times 10^{-6}$	Present study

Table 2: Interference Limits of Various Species in the Measurement of Sildenafil Citrate

(A) Species	[A]/Sildenafile
Ca^{2+}	1500
Hg^{2+}	1
Mg^{2+}	150
Ni^{2+}	152
K^{+}	574
Fe^{3+}	9
Pb^{2+}	0.2
Zn^{2+}	0.7
Co^{2+}	100
Glucose	39
Sucrose	150
Lactose	300
Starch	30
Citosan	50

4. Conclusion

This study demonstrates the efficacy of citrate-coated silver nanoparticles (AgNPs) as a colorimetric sensor for quantifying Sildenafil Citrate. Compared to conventional analytical methods, this sensor offers significant advantages, including simplicity, cost-effectiveness, rapid analysis, and minimal sample preparation, while maintaining high sensitivity and selectivity. Key parameters influencing sensor performance—such as the volume fraction of AgNPs, buffer composition, environmental pH, and reaction time—were optimized to achieve maximum sensitivity. The sensor exhibits a linear detection range of 0.34–3.1 µM and an impressive detection limit of 0.005 µM. Successful application of the sensor to quantify Sildenafil Citrate in pharmaceutical samples confirms its robustness, accuracy, and potential as a reliable method for quality control in health product analysis.

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

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Authors Contribution

Maryam Bordbar: Supervisor, Design the idea and the manuscript's structure, Writing the manuscript, Editing the manuscript.
Atieh Mohammadmirzaei: MSc Student, Writing the manuscript.

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