Detailed Kinetic and Mechanistic Study for the Preparation of Silver Nanoparticles by a Chemical Reduction Method in the Presence of a Neuroleptic Agent (Gabapentin) at an Alkaline pH and its Characterization

Bushra Yaseen, Chinky Gangwar, Indresh Kumar, Joy Sarkar, and Radhey Mohan Naik

ABSTRACT: For the very first time, a detailed kinetic study for the preparation of silver nanoparticles (silver NPs) by neuroleptic agent gabapentin (GBP) in the absence of a stabilizer has been reported in this investigation. This paper is devoted to the preparation of silver nanoparticles by a chemical reduction method in which gabapentin acts as both a reductant and a stabilizer, and AgNO₃ is used as a source of Ag⁺ ions and NaOH for maintaining the alkaline medium. A UV–visible spectrophotometer is used to monitor the progress of the reaction kinetics in an aqueous medium by changing the concentration of different variables such as AgNO₃, NaOH, and gabapentin at 40 °C. It is found that the reaction rate follows a pseudo-first-order reaction. The thermodynamic activation parameters were also studied at five different temperatures (303, 308, 313, 318, and 323 K) and used in the support of the proposed mechanistic scheme for the formation of silver nanoparticles. The prepared silver nanoparticles were characterized using different techniques: UV–visible spectrophotometry, Fourier transform infrared spectroscopy, field emission scanning electron microscopy, energy-dispersive X-ray spectroscopy, transmission electron microscopy, and powder X-ray diffraction. The average particle size was observed in the range of 5–45 nm.

1. INTRODUCTION

The era of synthesis of nanoparticles has played a very crucial role in enhancing the existing field of nanotechnology. During the last few decades, there has been a surge of interest in understanding the concept of nanoparticles and their application in various fields. Nanoparticles that encompass a wide class of nanotechnology include particulate substances having at least one dimension less than 100 nm. These nanoparticles are not like simple molecules; rather, they are composed of three different layers, viz., surface layer, shell layer, and core. They also exist in different shapes and sizes and can be free and composed of inorganic or organic moieties. Due to their extremely small size and large surface-area-to-volume ratio, their physical and chemical properties vary in the surface and bulk with the same composition. They show a huge variation in their shape and size, due to which they exhibit a broad range of applications in different areas such as catalysis, biosensing, biological activity, drug delivery, electronics, and also in the field of medicine, pharmacy, and so on.

In the field of nanomaterials, metal nanoparticles have received much importance due to their uniform size distribution. They are exclusively made up of metal precursors and have well-known surface plasmonic resonance (SPR) bands in localized regions. Among all of the metal nanoparticles, noble metal nanoparticles (Ag, Au, and Pt), especially Ag and Au nanoparticles, have received increasing attention due to their high surface-area-to-volume ratio, ease of synthesis, and feasible surface chemistry. These metal nanoparticles also present high tunable and optical properties, which can be tuned easily to the desired wavelength. The SPR range of noble metal nanoparticles mainly appears in the visible region due to which they exhibit applications in several regions such as colorimetric sensors, catalysis, bioimaging, environmental remediation, and cancer therapy. Compared to all of the noble metal nanoparticles (Au and Ag), silver nanoparticles (silver NPs) have quite surprisingly achieved great importance and are the most intensively studied.
noble metal nanoparticles due to their peculiar properties exhibited in the biological field.\textsuperscript{17,18} They are extensively studied and highly commercialized as they are much cheaper than AuNPs and widely used in consumer products, such as personal care products, cosmetics, medicinal devices, textile industries, and cleansing agents.\textsuperscript{19} All of the peculiar properties and applications related to silver NPs mentioned above inspired us to synthesize silver NPs.

There are a number of reports available in connection with the synthesis of silver NPs via different methods such as photochemical/electrochemical reduction,\textsuperscript{20} microwave-assisted synthesis,\textsuperscript{21} laser ablation,\textsuperscript{22} irradiation,\textsuperscript{23} ultrasound processing,\textsuperscript{24} chemical reduction,\textsuperscript{25} etc. In all of the above-mentioned methods, it was observed that the chemical reduction method is superior for the preparation of silver NPs. This method can synthesize silver NPs of different morphologies, and it is cost-effective and can easily be scaled up for large-scale preparation without involving high pressure, energy, and temperature. The synthesis of silver NPs mainly depends on experimental conditions such as temperature, pH, concentration, and the nature of the reducing agent. This method involves the synthesis of silver NPs from silver nitrate solution using various reductants. These reductants can be any organic/inorganic compound, base, amino acid, carbohydrate, medicine,\textsuperscript{26−29} etc.

Since previous studies have revealed that the reductant can be of any nature, thus in the present investigation for the preparation of silver NPs, we have chosen a chemical reduction method for the synthesis of silver NPs in which neuroleptic drug gabapentin (GBP) was used as a reductant for the preparation of silver NPs. GBP is 1-(aminomethyl) cyclohexyl acetic acid having a chemical formula C\textsubscript{9}H\textsubscript{17}NO\textsubscript{2},\textsuperscript{30} also known as cyclohexyl acetic acid,\textsuperscript{31} and an anticonvulsant drug having two functional groups,\textsuperscript{32} −NH\textsubscript{2} and −COOH. In the market, GBP is available under different brand names, such as Gralise, Neurontin, Fanatrex, and Horizant.\textsuperscript{33} GBP is an anticonvulsant agent that is used for the treatment of epileptic seizures with an estimated 4−10 persons per 1000 people in the general population.\textsuperscript{34} The structural representation of GBP is given in Figure 1. Clinical studies suggest that GBP is found to be effective in treating neuropathic pain associated with cancer and HIV infection and diabetic neuropathy.\textsuperscript{34} Subsequently, it was shown to be effective in treating severe dreadful surgical pain, postoperative analgesia, postherpetic neuralgia, and reflex sympathetic dystrophy.\textsuperscript{35} It is also used in the treatment of various psychiatric and migraine disorders. GBP is also found to be efficient in curing symptoms related to vasomotor.\textsuperscript{36} Some of the clinical trials suggest that GBP is also used for the treatment of alcohol dependence.\textsuperscript{37} Not only this, GBP in combination with some other medicines represents add-on therapy. GBP in combination with baclofen was found to be effective for idiopathic chronic hiccup (ICH) treatment.\textsuperscript{38}

GBP coupled with dexamethasone is used for the treatment of brain tumors.\textsuperscript{39} In combination with a placebo group, GBP is found to be effective in the treatment of refractory partial seizures. It is soluble in acidic and alkaline media. At physiological pH, it was found that GBP acts as both a reducing and a stabilizing agent.\textsuperscript{30,33,40−48}

In this paper, we have reported the formation of highly stable silver NPs by a chemical reduction method in the presence of GBP which acts as both a reductant and a stabilizer in an alkaline medium at 40 °C. To the best of our knowledge, till date, growth kinetic and thermodynamic activation parameter studies on the synthesis of silver NPs using GBP as a reductant have not been reported. The growth kinetics of formation of silver NPs was studied using a double beam UV−visible spectrophotometer at 415 nm (lambda max of silver NPs), and the synthesis of silver NPs was further confirmed using Fourier transform infrared (FT-IR) spectroscopy, field emission scanning electron microscopy (FESEM), energy-dispersive X-ray (EDAX) spectroscopy, transmission electron microscopy (TEM), and powder X-ray diffraction (PXRD).

2. PREPARATION AND CHARACTERIZATION OF SILVER NANOPARTICLES

For the preparation of silver NPs, a chemical reduction method was employed, which involves the reduction of Ag\textsuperscript{+} to elemental silver NPs by GBP. GBP acts as both a reductant and a stabilizer in an alkaline medium because stable silver NPs cannot be produced in an acidic or neutral condition due to the presence of pH-sensitive groups, −COOH and −NH\textsubscript{2} groups.\textsuperscript{40} All of the stock solutions (AgNO\textsubscript{3}, GBP, and NaOH) were prepared using double-distilled deionized water, thermally equilibrated at least for an hour at 40 °C in a thermostat, and subsequently used under specified reaction conditions. The glassware was cleaned with regal water and finally rinsed with doubly distilled deionized water before use. The best condition was obtained when the color of the reaction mixture changed from colorless to pale yellow by the addition of reagents in the sequence of GBP, NaOH, and then AgNO\textsubscript{3} in the alkaline medium at 40 °C. Subsequently, the color of the reaction mixture became brownish-yellow\textsuperscript{41} overnight, and then the brown color was more intensified with time, as shown in Figure 2a. To confirm the nature of the brownish-yellow silver NPs formed, the spectrum of the reaction mixture was recorded at different time intervals. The characteristic feature of the spectrum of the silver NPs so formed is a narrow plasmon absorption band observed in the 340−560 nm region. The highest absorption peak due to the plasmon absorption band of the silver NPs colloid at 415 nm in the visible SPR region is obtained, which confirms the presence of silver NPs.\textsuperscript{32} The intense peak observed at 200 nm\textsuperscript{3} is attributed to the reducing agent GBP, which facilitates the reduction of Ag\textsuperscript{+} to elemental silver NPs. The formation of silver NPs is shown in Figure 2b with an inset graph representing no change in the peak position with time between 0 and 100 min. To test the stability of silver NPs, the colloidal silver NPs were kept for more than a month. It was noticed that there was no change in the peak of absorption and it remained constant at 415 nm, but when kept for longer, after a few days, we observed the formation of a silver mirror on the walls of the test tube as shown in Figure 2c. The formation of the silver mirror was too slow, which suggested that most of the particles existed in the highly stable silver NPs form and confirmed the stability\textsuperscript{42} of the synthesized silver NPs. The prepared silver NPs were

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{COOH} \\
\end{align*}
\]

Figure 1. Structural representation of gabapentin (GBP).
extremely stable, remaining without any observable change in the peak for more than a month at room temperature and without any conservation from light, suggesting the formation of only spherical silver NPs. The flow chart given in Figure 3 exhibits a systematic representation for the synthesis and kinetic study of silver NPs.

Figure 2. (a) Change in the intensity of the color of silver nanoparticles colloid kept for more than a month (photograph courtesy of “B.Y.” Copyright 2019); (b) absorption spectra of pure gabapentin and silver nanoparticles with the inset graph showing plots for the reaction conditions [AgNO₃] 0.02 mM, [NaOH] 0.015 mM, and [GBP] 3.0 μM at different time intervals (0−100 min); and (c) formation of a silver mirror (photograph courtesy of “B.Y.” Copyright 2019).

Figure 3. Flow chart showing a systematic representation of the preparation and growth kinetic study of silver NPs.

3. RESULTS AND DISCUSSION
Preliminary observations show that pH plays a prime role in the preparation of silver NPs via GBP. GBP, which is a reducing agent, has a structural resemblance with γ-amino acid due to the presence of −COOH and −NH₂ groups and in aqueous solution exists in cationic, zwitter ion, and anionic forms in equilibrium. The stability of the silver NPs colloid is
pH-dependent, and its growth kinetics can be stopped by the addition of even a small amount of mineral acid.\textsuperscript{50} On this account, the control of pH is crucial for silver NPs formation, which was investigated first. GBP reduces Ag\textsuperscript{2+} ions into elemental silver NPs only at higher pH, and it has been found that in the absence of NaOH, no silver NPs colloid formation was observed. Therefore, NaOH was found to be important in the formation of silver NPs. The reaction was carried out at an elevated temperature of 40 °C, as it was observed that at room temperature reduction of Ag\textsuperscript{2+} ions into elemental silver NPs via GBP was very slow and the colorless mixture becomes turbid yellow with time; therefore, the reaction was carried out at an elevated temperature, i.e., 40 °C, to remove this turbidity and increase the rate of the reaction.

For the kinetic study, all of the reaction mixtures were equilibrated at 40 °C for about an hour. Then, a requisite volume of all of the reagents except AgNO\textsubscript{3} was taken in a double-necked reaction vessel. The reaction was started with the addition of the desired volume of AgNO\textsubscript{3} solution. Zero time was taken for the AgNO\textsubscript{3} solution to be poured into the reaction vessel. The progression of the reaction was monitored spectrophotometrically by pipetting out the reaction mixture at an interval of 10 min in the presence or absence of surfactant, and the absorbance was estimated at a fixed wavelength of 415 nm. In the course of the reaction, the color of the reaction mixture changed from colorless to pale yellow. In the current study, kinetic runs were performed as a function of [AgNO\textsubscript{3}] from 0.01 ≤ [AgNO\textsubscript{3}] ≤ 0.035 mM with 0.015 mM [NaOH] and 3.00 μM [GBP], as a function of [NaOH] from 0.01 ≤ [NaOH] ≤ 0.035 mM with 0.02 mM [AgNO\textsubscript{3}] and 3.0 μM [GBP], and as a function of [GBP] 1.00 ≤ [GBP] ≤ 6.00 μM with 0.015 mM [NaOH] and 0.02 mM [AgNO\textsubscript{3}]. The pseudo-first-order condition was maintained by taking [AgNO\textsubscript{3}] and [NaOH] in excess over [GBP]. Therefore, the kinetics of the reaction totally depends on [GBP]. The pseudo-first-order rate constant was obtained from the slope of the linear plot between lnA and time with the correlation coefficient (adj. R\textsuperscript{2} = 0.998).

Triplicate runs for each concentration were performed, which gave a result reproducible within ±5%. It was observed that the pH remained the same throughout or changed by only 0.05 units when measured for each concentration at the inception and the extremity of the reaction.

3.1. Characterization. 3.1.1. Fourier Transform Infrared (FT-IR) Spectroscopy. FT-IR analysis was performed in the range of 4000–1000 cm\textsuperscript{-1}, as shown in Figure 4, to determine the functional group attached to the synthesized silver NPs. For the synthesized silver NPs, three different FT-IR bands were obtained at wavenumbers 1392, 1651, and 3422 cm\textsuperscript{-1}, which correspond to COO\textsuperscript{-}, >C=O stretching, and the stretching of –OH groups, respectively.\textsuperscript{55}

3.1.2. FESEM and EDAX Analyses. Morphological studies including the structure and size of the prepared silver NPs were performed using FESEM. FESEM images at two different magnifications, 80,000 and 2,00,000, were taken and are shown in Figure 5a,b. The silver NPs have spherical morphology, and a few silver NPs were agglomerated.\textsuperscript{56} The average particle size was calculated using ImageJ software and found to be around 27.11 nm.

Furthermore, the elemental composition of each element present in the prepared sample was also inspected using energy-dispersive X-ray analysis. The EDAX analysis exhibits an intense peak at 3.00 eV for 53.19% Ag revealing the formation of silver NPs, as shown in Figure 5c. Along with Ag, carbon and oxygen peaks were also obtained having a weight composition of 5.89% for carbon and 40.92% for oxygen, as shown in the scatter diagram in Figure 5d. The prominent peak of oxygen reveals that a few of the silver ions react with atmospheric oxygen leading to the formation of the Ag\textsubscript{2}O phase. It is indispensable to mention that a strong signal was noticed at 1.49 eV as the sample was coated on the (SiO\textsubscript{2}) silicon substrate.

3.1.3. Transmission Electron Microscopy. To understand the accurate morphology and size of the prepared silver NPs, TEM analysis was performed. The solution of silver NPs was sonicated prior to TEM examination. For TEM analysis, the synthesized solution of silver NPs was dropped on a carbon-coated copper grid, and then the grid was dried at room temperature. TEM images at two different magnifications, 50 nm and 20 nm, were taken as shown in Figure 6a,b. The silver NPs have spherical morphology, and a few of the silver NPs were aggregated. The TEM images clearly show nanostructure homogeneities with spherical morphologies of silver NPs. The TEM analysis shows a good resemblance with the FESEM result with morphology and particle size. There was a slight deviation in the particle size estimated from PXRD analysis, which suggests deviation of the spherical shape of the particles that is required for the Debye–Scherer formula and the detection limit of the PXRD diffractometer.\textsuperscript{57} A histogram containing 73 silver NPs was used to calculate the average particle size, which was about 24.09 nm, using ImageJ software, as shown in Figure 6c, with a size distribution between 5 and 45 nm.

3.1.4. Powder X-ray Diffraction Analysis. The crystalline nature of the prepared silver NPs was confirmed by the powder X-ray diffraction pattern (PXRD). Figure 7 shows the PXRD pattern of the synthesized silver NPs, which confirms the formation of silver NPs during the course of synthesis. Six discrete diffraction patterns at 2θ values of 33.33° (1 1 1), 38.67° (1 1 1), 42.30° (2 0 0), 48.0° (2 0 0), 55.73° (1 1 2), and 60.73° (2 2 0) were obtained due to silver NPs, which matched with the pure crystalline silver structure database of the Joint Committee on Powder Diffraction Standards (JCPDS) file no. (75-1352).\textsuperscript{56,61} Besides these, two more peaks at 34.00° (1 1 1) and 66.45° (3 1 1) were obtained represented by * matching with the Joint Committee on Powder Diffraction Standards (JCPDS) file no. (75-1352).\textsuperscript{56,61} for the Ag\textsubscript{2}O phase. The most intense peak was obtained at (1 1 2) due to silver NPs. From the PXRD plot, we can conclude that most of the peaks obtained are related to silver NPs and only a few peaks are related to Ag\textsubscript{2}O phase, from which we can

Figure 4. FT-IR spectra of silver nanoparticles.
conclude that the silver NPs were formed in a larger amount and some of them were converted into the Ag$_2$O phase. The formation of the Ag$_2$O phase helps in the nucleation of silver NPs, as shown in the mechanism. The mean average crystallite size was evaluated using the Debye–Scherer formula represented by eq 1, where $D$ is the average crystallite size, $\lambda$ represents the wavelength, and $\theta$ represents Bragg’s angle. The mean average crystallite size from the Debye–Scherer method was found to be around $\sim 15.40$ nm from the most intense peak.

$$D = \frac{0.9\lambda}{\beta \cos \theta}$$  \hspace{1cm} (1)

$$\beta \cos \theta = k\lambda / D + 4\varepsilon \sin \theta$$  \hspace{1cm} (2)

3.2. Optimization of Different Variables for the Kinetic Study of Prepared Silver Nanoparticles. To determine the optimized condition for all of the reacting species involved in the kinetics of silver NPs colloid formation, the reaction was performed at different concentrations for each variable by changing the concentration of one variable at a time while keeping the concentration of other variables constant at the same time. During the reaction, the color of the reaction mixture changed from colorless to pale yellow and then brownish-yellow. In the current study, kinetics runs were performed as a function of [AgNO$_3$] from $0.01 \leq$ [AgNO$_3$] $\leq 0.035$ mM with $0.015$ mM [NaOH] and $3.0$ μM [GBP], as a function of [NaOH] from $0.01$ mM $\leq$ [NaOH] $\leq 0.04$ mM with $0.02$ mM [AgNO$_3$] and $3.0$ μM [GBP], and as a function of [GBP] from $1.00 \leq$ [GBP] $\leq 6.00$ μM with $0.015$ mM [NaOH] and $0.02$ mM [AgNO$_3$]. The progress of the reaction was monitored spectrophotometrically as a function of time between 0 and 100 min at a particular wavelength ($\lambda_{\text{max}} = 415$ nm) of silver NPs. The best result after optimization of each condition was obtained with [NaOH] = $0.015$ mM, [AgNO$_3$] = $0.02$ mM, and [GBP] = $3.00$ μM having a regression coefficient (adj. $R^2$) value of 0.998. The pseudo-first-order rate constant ($k_{\text{obs}}$) was estimated from the slope plot $\ln A$ versus time at 415 nm as shown in Table 1. The integrated rate expressions for growth kinetics for the formation of silver NPs colloid is given by eq 3.

$$A = A^0 e^{k_{\text{obs}} t}$$  \hspace{1cm} (3)

The logarithm form of eq 3 is given by eq 4

$$\ln A = \ln A^0 + k_{\text{obs}} t$$  \hspace{1cm} (4)

or

$$\ln(\text{absorbance})_t = \ln(\text{absorbance})_{t=0} + k_{\text{obs}} t$$  \hspace{1cm} (5)

3.2.1. NaOH Optimization. NaOH plays a very important role during the reaction, maintaining alkaline pH and increasing the reduction of Ag$^+$ ions into elemental silver NPs. It was observed that at low pH values due to the availability of excess H$^+$ ions, the reaction was stopped; therefore, an alkaline medium is important for the synthesis of silver NPs.
silver NPs colloid. It is significant to mention that in the absence of NaOH, there was no formation of silver NPs colloid. The effect of [NaOH] on the rate of formation of silver NPs colloid was considered to be between 0.01 ≤ [NaOH] ≤ 0.035 mM with 0.02 mM [AgNO₃] and 3.00 μM [GBP] at 415 nm and a fixed temperature of 40 ± 1 °C. Above the concentration of 0.03 mM, the growth kinetic study did not proceed as on further addition of NaOH in the reaction mixture, the value of absorbance with time decreased and became constant. The exponential growth curve was obtained when absorbance versus time was plotted for different concentrations of [NaOH], as shown in Figure 8a. The rate constant of the prepared silver NPs colloid was estimated from the slope of the lnA versus time plot at 415 nm, as shown in Figure 8b. From the plot given in Figure 8b, it is clear that the value of the rate constant (k_{obs}) for [NaOH] varied in the range from 0.01 to 0.02 mM, gradually decreasing from 12.63 × 10⁻³ and 6.17 × 10⁻³ to 5.12 × 10⁻³ min⁻¹ having the regression coefficient (adj. R²) values of 0.993, 0.998, and 0.994, respectively. Above this concentration at 0.025 mM, the rate constant again increases and then decreases for 0.03 mM from 8.74 × 10⁻³ to 7.42 × 10⁻³ min⁻¹ with the regression coefficient (adj. R²) values of 0.987 and 0.970, respectively.

Figure 6. TEM image of silver NPs: (a) 50 nm and (b) 20 nm and (c) histogram representation of silver NPs.

Figure 7. Powder X-ray diffraction pattern for silver nanoparticles.

Table 1. Values of k_{obs} as a Function of [NaOH], [GBP], [AgNO₃], and pH Values

| [NaOH], mM | [GBP], μM | [AgNO₃], mM | pH | k_{obs} (×10⁻³ min⁻¹) | adj. R² |
|------------|-----------|-------------|----|------------------------|--------|
| 0.01       | 3.00      | 0.02        | 11.20 | 12.62                  | 0.993  |
| 0.015      | 3.00      | 0.02        | 11.30 | 6.17                   | 0.998  |
| 0.02       | 3.00      | 0.02        | 11.32 | 5.21                   | 0.994  |
| 0.025      | 3.00      | 0.02        | 11.33 | 8.74                   | 0.987  |
| 0.03       | 3.00      | 0.02        | 11.45 | 7.42                   | 0.970  |
| 0.015      | 1.00      | 0.02        | 11.52 | 7.95                   | 0.982  |
| 0.015      | 2.00      | 0.02        | 11.65 | 6.87                   | 0.925  |
| 0.015      | 3.00      | 0.02        | 11.30 | 6.17                   | 0.998  |
| 0.015      | 4.00      | 0.02        | 11.92 | 5.26                   | 0.952  |
| 0.015      | 5.00      | 0.02        | 11.98 | 4.49                   | 0.896  |
| 0.015      | 3.00      | 0.01        | 11.53 | 2.4                    | 0.983  |
| 0.015      | 3.00      | 0.015       | 11.45 | 3.5                    | 0.994  |
| 0.015      | 3.00      | 0.02        | 11.30 | 6.17                   | 0.998  |
| 0.015      | 3.00      | 0.025       | 11.29 | 2.2                    | 0.995  |
| 0.015      | 3.00      | 0.03        | 11.18 | 4.3                    | 0.990  |
The observed decrease, increase, and then again decrease in the value of the rate constant might be because a small amount of NaOH was enough for the reduction of Ag⁺ ions by GBP. It might also be due to the formation of zwitterion in equilibrium with neutral GBP structure.

From the above discussion, it can be inferred that at higher NaOH concentrations, the rate constant decreases due to the high concentration of OH⁻ ions in the solution. Therefore, it is important to mention that the rate of the reaction is sensitive to [OH⁻], and even at a lower concentration of OH⁻ ion, a small amount of NaOH is sufficient for the nucleation of the silver NPs colloid from Ag⁺ ions.

3.2.2. Gabapentin Optimization. The best condition of GBP for reduction of Ag⁺ ion into elemental silver NPs has been obtained under the optimized condition of pH of the reaction medium. It has been found that GBP acts only at higher pH mainly in alkaline medium. To maintain this alkaline medium, a concentrated NaOH solution was used during the preparation of the stock solution of GBP. The effect of [GBP] on the rate of formation of silver NPs colloid was studied between 1.00 ≤ [GBP] ≤ 6.00 μM with 0.02 mM [AgNO₃] and [NaOH] 0.015 mM at 415 nm and at a fixed temperature of 40 ± 0.1 °C, respectively. The growth kinetics was not observed above this concentration due to turbidity, which caused an abrupt change in the value of absorbance. The exponential growth curve was obtained when absorbance versus time was plotted for different [GBP], as shown in Figure 9a. The pseudo-first-order rate constant \( k_{\text{obs}} \) for the formation of silver NPs colloid was calculated from the plot of lnA versus time at 415 nm, as shown in Figure 9b. It was observed that there was a continuous gradual decrease in the \( k_{\text{obs}} \) value on increasing [GBP] from 1.00 to 5.00 μM. The rate constant was found to be 7.95 × 10⁻³, 6.87 × 10⁻³, 5.17 × 10⁻³, 5.26 × 10⁻³, and 4.49 × 10⁻³ min⁻¹ for 1.00, 2.00, 3.00, 4.00, and 5.00 μM [GBP], respectively. The value of regression coefficient (adj. \( R^2 \)) for each [GBP] was found to be 0.982, 0.925, 0.998, 0.952, and 0.896, respectively. The continuous decrease in the value of the rate constant \( k_{\text{obs}} \) for GBP might be attributed to the agglomeration or flocculation of silver NPs colloid at higher concentrations of GBP or to the adsorption of GBP or its oxidized product on the surface of nanoparticles, which shows a good resemblance with FT-IR analysis and EDAX analysis (vide supra). It can now be stated that only a small amount of GBP is sufficient for the reduction of Ag⁺ ions present in the reaction mixture.

3.2.3. AgNO₃ Optimization. To study the effect of [AgNO₃] on the formation of silver NPs colloid under optimized reaction conditions at 415 nm and at a fixed temperature of 40 ± 1 °C, different sets of [AgNO₃] varying from 0.01 ≤ [AgNO₃] ≤ 0.035 mM were used. The growth kinetic study above this concentration was inhibited due to formation of a gray precipitate, which causes hindrance while recording the values of absorbance on the spectrophotometer. After the variation, an exponential growth curve was obtained when absorbance versus time was plotted for different [AgNO₃] at a fixed wavelength of 415 nm, as shown in Figure 10a. The rate constant \( k_{\text{obs}} \) for the formation of silver NPs colloid was calculated from the slope of the lnA versus time plot at different [AgNO₃] at 415 nm, as shown in Figure 10b. From this plot, it is clear that for [AgNO₃] ranging from 0.01...
Figure 10. (a) Absorbance versus time plot at 3.0 μM [GBP] and 0.015 mM [NaOH] as a function of [AgNO₃] at 415 nm and (b) plot of lnA versus time at 3.0 μM [GBP] and 0.015 mM [NaOH] as a function of [AgNO₃] at 415 nm varying from 0.01 ≤ [AgNO₃] ≤ 0.035 mM.

Scheme 1. Proposed Mechanism for the Formation of Silver Nanoparticle Colloid

\[ \text{Ag}_2\text{O} + (\text{Ag})_n \xrightarrow{\text{fast}} \text{Ag}_2\text{O} - (\text{Ag})_n \]  

\[ \text{Ag}_2\text{O} - (\text{Ag})_n + \xrightarrow{k_{\text{red}}} \text{H}_2\text{N}^{+}\text{C} = \text{CH}_2\text{C}O\text{O}^- + \text{Ag}_2\text{O} - (\text{Ag})_n \]  

\[ \text{Ag}_2\text{O} - (\text{Ag})_n + \xrightarrow{\text{radical}} \xrightarrow{\text{fast}} \text{H} = \text{C} = \text{CH}_2\text{C}O\text{O}^- + \text{Ag}_2\text{O} - (\text{Ag})_n \]  

\[ \text{Ag}_2\text{O} - (\text{Ag})_n \xrightarrow{\text{radical}} \text{Ag}_2\text{O} - (\text{Ag})_n \]  

\[ \epsilon^- (\text{Ag}_2\text{O}) \]  

\[ \epsilon^- (\text{Ag}_2\text{O}) + \xrightarrow{\text{fast}} \text{Ag}^0 \]  

\[ \text{Ag}^0 + \xrightarrow{\text{fast}} \text{Ag}_2^+ \]  

\[ \text{Ag}_2^+ + \xrightarrow{\text{fast}} \text{Ag}_4^{2+} \]  

\[ (\text{Ag}_4^{2+})_n + (\text{GBP})_n \xrightarrow{\text{fast}} \text{Yellowish Brown AgNPs colloid} \]  

\[ \text{(Nucleation)} \]  

\[ \text{(Growth)} \]  

\[ \text{Adsorption} \]
GBP shows structural resemblance with amino acids due to the alkaline medium as given in Scheme 1 through eqs 6

preparation of silver NPs colloid by GBP reductant in an alkaline medium. As given in Scheme 1 through eqs 6–14. As GBP shows structural resemblance with amino acids due to the presence of −NH₂ and −COOH, on oxidation, it particularly gives CO₂, ammonia, and the corresponding aldehydes shown in different steps in the given mechanism. The mechanism given in Scheme 1 is a two-electron transfer process in which Ag⁺ ions react with the reducing agent GBP in an alkaline medium and are reduced into the elemental Ag state and the reducing agent GBP is oxidized into the corresponding aldehyde. The first reaction in Scheme 1, eq 6, is nucleation, which involves the reduction of Ag⁺ ions into elemental Ag by the reductant GBP in presence of OH ions produced from NaOH, and fast formation of colloidal Ag₂O phase occurs which helps in the adsorption of Ag⁺ ions on the surface of Ag₂O phase. The complexation of Ag₂O with Ag⁺ leads to the formation of the (Ag₂O–Ag⁺) complex in eq 7, which on further reaction with the moiety (A) given in eq 6 leads to the generation of the radical shown in eq 8. The generation of the radical is the slowest step and the rate-determining step. It was observed that all of the Ag⁺ ions were not converted into the Ag⁰ form and some of them were converted into the oxide form, Ag₂O, which is supported by EDAX and PXRD data, as shown in Figures 5d and 6. Adsorption of Ag⁺ ions starts taking place on the surface of Ag₂O, as shown in eq 7. The resulting species then reacts with the radical and leads to the formation of the oxidized product of GBP and a nucleophilic species Ag₂O–(Ag⁺), in eq 9. This nucleophilic species was then converted into e⁻Ag₂O in eq 10. After this step, nucleation takes place again when e⁻Ag₂O reacts with Ag⁺ ions leading to the formation of Ag⁰ in eq 11. The growth of the silver NPs colloid is shown by eqs 12 and 13. At the end of the reaction, GBP is adsorbed on the (Ag₂O) surface and brownish-yellow silver NPs colloid shown in eq 14 was formed.

3.2.4. Plausible Mechanism Proposed for the Formation of Silver Nanoparticles. On the basis of experimental findings, a most plausible mechanism has been proposed for the preparation of silver NPs colloid by GBP reductant in an alkaline medium as given in Scheme 1 through eqs 6–14. As GBP shows structural resemblance with amino acids due to the presence of −NH₂ and −COOH, on oxidation, it particularly gives CO₂, ammonia, and the corresponding aldehydes shown in different steps in the given mechanism. The mechanism given in Scheme 1 is a two-electron transfer process in which Ag⁺ ions react with the reducing agent GBP in an alkaline medium and are reduced into the elemental Ag state and the reducing agent GBP is oxidized into the corresponding aldehyde. The first reaction in Scheme 1, eq 6, is nucleation, which involves the reduction of Ag⁺ ions into elemental Ag by the reductant GBP in presence of OH ions produced from NaOH, and fast formation of colloidal Ag₂O phase occurs which helps in the adsorption of Ag⁺ ions on the surface of Ag₂O phase. The complexation of Ag₂O with Ag⁺ leads to the formation of the (Ag₂O–Ag⁺) complex in eq 7, which on further reaction with the moiety (A) given in eq 6 leads to the generation of the radical shown in eq 8. The generation of the radical is the slowest step and the rate-determining step. It was observed that all of the Ag⁺ ions were not converted into the Ag⁰ form and some of them were converted into the oxide form, Ag₂O, which is supported by EDAX and PXRD data, as shown in Figures 5d and 6. Adsorption of Ag⁺ ions starts taking place on the surface of Ag₂O, as shown in eq 7. The resulting species then reacts with the radical and leads to the formation of the oxidized product of GBP and a nucleophilic species Ag₂O–(Ag⁺), in eq 9. This nucleophilic species was then converted into e⁻Ag₂O in eq 10. After this step, nucleation takes place again when e⁻Ag₂O reacts with Ag⁺ ions leading to the formation of Ag⁰ in eq 11. The growth of the silver NPs colloid is shown by eqs 12 and 13. At the end of the reaction, GBP is adsorbed on the (Ag₂O) surface and brownish-yellow silver NPs colloid shown in eq 14 was formed.

3.3. Study of Thermodynamic Activation Parameters. The formation of silver NPs was studied at five different temperatures, 303, 308, 313, 318, and 323 K, under the reaction conditions of 0.02 mM [AgNO₃], 0.015 mM [NaOH], and 3.00 μM [GBP]. All of the values for the thermodynamic activation parameters were calculated at 40 °C. The values of the reported thermodynamic activation parameters, i.e., enthalpy change of activation (ΔH°) and entropy change of activation (ΔS°), were evaluated using the Eyring equation, eq 15

$$\ln \left( \frac{k_{obs}}{k_B T} \right) = \frac{\Delta S^\circ}{R} - \frac{\Delta H^\circ}{RT}$$

(15)

where kₒ is Boltzmann constant, k represents the rate constant, h represents Planck’s constant, and R represents the gas constant. Enthalpy change of activation (ΔH°) and entropy change of activation (ΔS°) were calculated from the slope and intercept value of the plot of ln (kₒ/κₐₜ) versus 1/T giving a straight line with the regression coefficient value equal to 0.973 as shown in Figure 11 and found to be 75.71 kJ mol⁻¹ and -222.40 J mol⁻¹ K⁻¹, respectively. The free energy change of activation (ΔG°) was also estimated from eq 16 and found to be 61.0 kJ mol⁻¹. The value of activation energy E° was evaluated using eq 17 and found to be 78.31 kJ mol⁻¹. The value of the equilibrium constant K° was calculated using eq 18 and found to be 9.59 × 10⁻².

$$\Delta G^\circ = \Delta H^\circ - T \Delta S^\circ$$

(16)

$$E^\circ = \Delta H^\circ + RT$$

(17)

$$\Delta G^\circ = -RT \ln K^\circ$$

(18)

These thermodynamic activation parameter data reveal the nature of interaction, spontaneity, and feasibility of the reaction. The negative value of entropy of activation suggests that the intermediate transition state is more ordered than the reactants. The positive value for energy of activation and enthalpy of activation implies that the formation of silver NPs colloid is achieved through the electrostatic interaction between nanoparticles and gabapentin.

4. CONCLUSIONS

In the present investigation, we have reported the formation of silver NPs utilizing GBP as a reductant and a most tentative mechanistic scheme has also been proposed for the formation of silver NPs for the first time as no such studies have been reported in the literature to date. GBP has been preferentially chosen for this work because of its wide medicinal use. It also acts both as a reductant and a stabilizer. The effect of the concentration of each variable [NaOH], [GBP], and [AgNO₃]...
on the formation of silver NPs was analyzed and optimized spectrophotometrically with a change in color from colorless to yellow and then brownish-yellow, having maximum absorbance at 415 nm. The proposed mechanism signifies that it is a two-electron transfer process, and the reaction follows pseudo-first-order kinetics. It can be concluded that the method adopted for the synthesis of silver NPs is simple, economical, and rapid. This work involves a reasonably good approach and may be useful in the large-scale synthesis of silver NPs. Lastly, due to the interaction of a pharmaceutical drug (GBP) with silver NPs, the higher drug loading capacity of the prepared silver NPs can have wide applications in drug delivery and diagnostics.

5. EXPERIMENTAL SECTION

5.1. Chemicals Required. All of the chemicals, AgNO₃ and NaOH, were purchased from Sigma and Aldrich and were used as received. GBP of Intas company was purchased from a local medical store near Lucknow University. Doubly distilled deionized water was used as a solvent throughout the reaction for preparing stock solutions. NaOH was used to maintain the pH value at 11.0 for GBP solution, which provides a physiological condition for the reduction of AgNO₃ at ambient temperature.

5.2. Instruments Required. A double beam UV–vis spectrophotometer of LAB UV next generation was used for the pH meter, Systronic pH meter (model 361), with an amalaged electrode was used for the pH measurements of all of the samples. An FT-IR spectrometer from ThermoScientific Nicolet 670 was used to measure the peaks of the prepared silver NPs. A field emission scanning electron microscope of JFEI, Nova Nano SEM-450, was used to confirm the morphology and elemental analysis of the prepared silver NPs. A transmission electron microscope, Talos machine, operating at 200 eV was used to determine the accurate morphology and average particle size of the prepared silver NPs. PXRD on a Rigaku, SmartLab 9 kW, rotating anode X-ray diffractometer using Cu Ka X-ray of wavelength 1.54 Å in the range of 20 equal to 30–70° was used to confirm the average particle size of the prepared silver NPs.

■ AUTHOR INFORMATION

Corresponding Author
Radhey Mohan Naik – Department of Chemistry, Lucknow University, Lucknow 226007 Uttar Pradesh, India; orcid.org/0000-0003-1782-9125; Email: radheynaik@gmail.com

Authors
Bushra Yaseen – Department of Chemistry, Lucknow University, Lucknow 226007 Uttar Pradesh, India
Chinky Gangwar – Department of Chemistry, Lucknow University, Lucknow 226007 Uttar Pradesh, India
Indresh Kumar – Department of Chemistry, Lucknow University, Lucknow 226007 Uttar Pradesh, India
Joy Sarkar – Department of Chemistry, Lucknow University, Lucknow 226007 Uttar Pradesh, India

Complete contact information is available at: https://pubs.acs.org/10.1021/acsomega.1c05499

Notes
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■ ABBREVIATIONS

silver NPs silver nanoparticles
Ag⁰ elemental silver
AuNPs gold nanoparticles
GBP gabapentin
UV–vis ultraviolet–visible
FT-IR Fourier transformed infrared
FESEM field emission scanning electron microscopy
TEM transmission electron microscopy
PXRD powder X-ray diffraction
EDAX energy-dispersive X-ray analysis
SPR surface plasmon resonance

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