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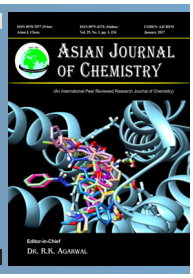

Synthesis of Platinum Nanoparticles Conjugates of Ceftriaxone and its Schiff Bases Using Sodium Borohydride and Trisodium Citrate

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The synthesis of platinum nanoparticles conjugates was achieved by the reduction of hexachloroplatinic acid with sodium borohydride ($NaBH_4$) and trisodium citrate in aqueous solutions using ceftriaxone and two Schiff base ligands derived from ceftriaxone sodium with 1H-indole-2,3-dione (isatin), L_1 and 1-acetyl indoline-2,3-dione (N-acetylisatin) L_2 as capping agents. The synthesized platinum nanoparticles were characterized by UV-visible spectrophotometry, X-ray diffraction, scanning electron microscope and atomic force microscope analysis. Conjugation of the ligands with the nanoparticles was characterized by FT-IR spectrophotometry.

Keywords: Ceftriaxone, Schiff base, Platinum nanoparticles, Surface plasmon resonance, $NaBH_4$, Trisodium citrate.

INTRODUCTION

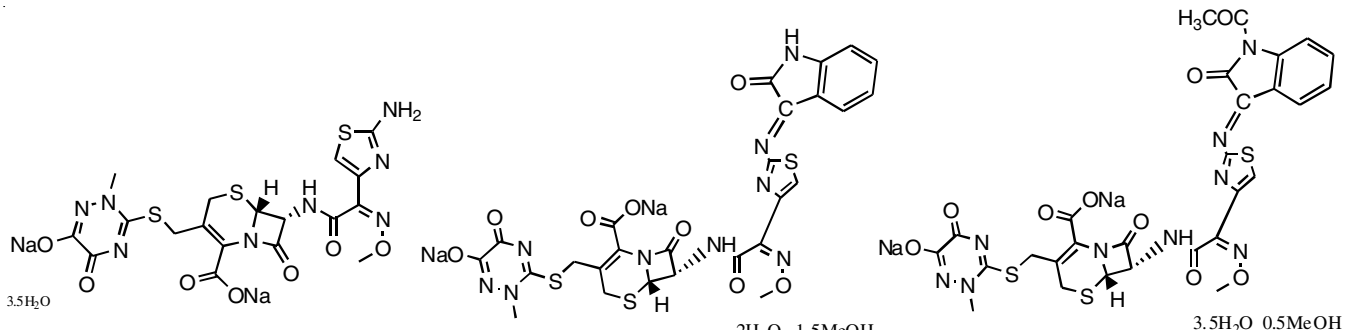
Platinum nanoparticles (PtNPs) have been extensively used in many applications such as catalysts in organic reactions (hydrosilylation, oxidation and hydrogenation [1,2] in fuel cells and in the exhaust systems of cars, cancer therapy, glucose sensors, electrochemical chemo- and biosensors and fluorescent sensors [3-6]. The catalytic properties of PtNPs strongly depend on their shape, size and surface area. The preparation of PtNPs by chemical reduction method includes the reduction of two or four valent platinum ions, using highly reactive chemicals such as hydrazine, sodium borohydride [7], ethylene glycol [4]. Different agents have been used as stabilizers for the synthesis such as, dendrimers, polyvinyl pyrrolidone [4], polyacrylic acid [8] and other polymers [7]. It was reported that platinum nanoparticles, in aqueous solution, had absorption spectra extended across the whole of the UV-visible region. A single unsteady absorption peak of surface plasmon absorption band in the UV spectrum region may appear between 200-280 nm [3]. In this work we investigated the synthesis of PtNPs conjugates by reduction of hexachloroplatinic acid (H_2PtCl_6) using sodium borohydride as a reducing agent and trisodium citrate as a stabilizing agent and the antibiotic ceftriaxone sodium and two Schiff bases derived from ceftriaxone sodium with 1H-indole-2,3-dione (isatin) (L_1) and 1-acetyl indoline-2,3-dione (N-acetylisatin) (L_2) (Fig. 1). The aim of this work is to study the conjugation of the ligand molecules on the surface of the synthesized PtNPs for drug delivery applications. The change in position and intensity of surface plasmon resonance band was studied spectrophotometrically in the UV-visible region. The PtNPs were characterized by FT-IR, SEM, AFM and XRD.

EXPERIMENTAL

The following chemicals were used as received from suppliers: ceftriaxone sodium ($C_{18}H_{16}N_8O_7S_3Na_2 \cdot 3.5H_2O$) (LDP), isatin (Aldrich), hexachloroplatinic acid ($H_2PtCl_6 \cdot 6H_2O$), trisodium citrate dihydrate ($C_6H_5O_7Na_3 \cdot 2H_2O$) and sodium borohydride ($NaBH_4$) (Fluka). The synthesis and characterization of the two Schiff base ligands was reported by us in a previous work [9].

Electronic spectra for prepared solutions in the (UV-visible) region (200-1100 nM) were recorded on Shimadzu 1800 double beam UV-visible spectrophotometer. The (FT-IR) spectra were obtained using Shimadzu FT-IR 8400S spectrophotometer. Separation of nanoparticles by centrifugation was carried out using Centerfuge C 41 7800 14000 rpm, Juan, (France). SEM images were acquired using (TescanVegaIIICZech) and (KYKY-EM3200). AFM images were obtained by using AA 3000 SPM 220 V-Angstrom Advanced INC. (USA). XRD analyses were performed using a Shimadzu XRD-6000 X-ray diffraction spectrometer.

Preparation of solutions: A stock aqueous solution of ceftriaxone (5.36×10^{-3} M) was prepared by dissolving 0.3546 g in 100 mL distilled deionized water (DDW). A standard aqueous solutions of ceftriaxone (2.68×10^{-3} M) was prepared by diluting 25 mL of stock solution to 50 mL of distilled



CR $[C_{18}H_{16}N_8Na_2O_7S_3.3.5H_2O]$ **L_1** $[C_{26}H_{19}N_9Na_2O_8S_3].2H_2O.1.5MeOH$ **L_2** $[C_{28}H_{21}N_9Na_2O_9S_3].3H_2O+0.5MeOH$

Fig. 1. Structures of ceftriaxon sodium and it's two Schiff base ligands [9]

deionized water in a 50 mL volumetric flask. Standard aqueous solutions of L_1 (2.62×10^{-3} M) and L_2 (2.68×10^{-3} M) were prepared by dissolving 0.2114 and 0.225 g, respectively in 100 mL of distilled deionized water in 100 mL volumetric flasks. A stock aqueous solution of $H_2PtCl_6 \cdot 6H_2O$ (3.276×10^{-2} M) was prepared by dissolving 0.1697 g of salt in 10 mL distilled deionized water. A standard solution of $PtCl_6^{2-}$ (2.13×10^{-2} M) was prepared by diluting 6.5 mL of stock solution to 10 mL with distilled deionized water. A standard aqueous solution of $NaBH_4$ (5.513×10^{-2} M) was freshly prepared by dissolving 0.05214 g of $NaBH_4$ in 25 mL cold distilled deionized water (10 °C). A stock aqueous solution of trisodium citrate ($C_6H_5O_7Na_3 \cdot 2H_2O$) ($5.389 \times 10^{-3}$ M) was prepared by dissolving 0.1585 g of trisodium citrate dihydrate in 100 mL distilled deionized water. A standard aqueous solution of trisodium citrate ($C_6H_5O_7Na_3 \cdot 2H_2O$) ($2.695 \times 10^{-3}$ M) was prepared by diluting 5 mL of stock solution to 10 mL by distilled deionized water.

Preparation of platinum nanoparticles using ceftriaxone antibiotic

An aqueous solution of H_2PtCl_6 (2.13×10^{-2} M, 1.63 mL), was added to an aqueous solution of ceftriaxone (2.68×10^{-3} M, 14 mL) under vigorous stirring and the mixture was cooled in an ice bath to 10 °C. Then an aqueous solution of $NaBH_4$ (5.513×10^{-2} M, 1.75 mL) which has been cooled to 10 °C was added slowly with continuous stirring. The colour of solution changed immediately to dark brown. Stirring was continued for 0.5 h. The absorbance of the solution was measured after 1 h.

To an aqueous solution containing trisodium citrate (2.695×10^{-3} M, 7mL) and ceftriaxone (2.68×10^{-3} M) cooled to 10 °C in an ice bath was added, a cold aqueous solution of $PtCl_6^{2-}$ (2.13×10^{-2} M, 1.63 mL) with continuous stirring. Then a cold solution of $NaBH_4$ (5.513×10^{-2} M, 1.75 mL) was added slowly. Stirring was continued for 0.5 h within which the colour of solution was changed to brown.

To an aqueous solution containing trisodium citrate (2.695×10^{-3} M, 7 mL) was added, an aqueous solution of $PtCl_6^{2-}$ (2.13×10^{-2} M, 1.63 mL) with continuous stirring. The mixture was cooled to10 °C in ice bath. Then a cold solution of $NaBH_4$ (5.513×10^{-2} M, 1.75 mL) was added slowly. The colour changed immediately to black indicating the formation of PtNPs. After 5 min at 10 °C, an aqueous solution of ceftriaxone (2.68×10^{-3} M, 7 mL) was added and stirring was continued for 0.5 h. The reaction mixture retained its black colour. The absorbance of the solution was measured after 1 h. The solution was subjected to centrifugation at 6000 rpm for 10-15 min. The residue was washed several times with acetone and finally dried with N_2 gas and kept for further analysis.

Preparation of PtNPs in presence of Schiff base ligands L_1 and L_2: To a cold aqueous solution of H_2PtCl_6 (2.13×10^{-2} M, 1.63 mL), in ice bath at (10 °C) was added, an aqueous solution containing sodium citrate ($C_6H_5O_7Na_3 \cdot 2H_2O$) ($2.695 \times 10^{-3}$ M, 7mL) and one of the two Schiff base ligands (L_1, 2.62×10^{-3} M or L_2, 2.68×10^{-3} M) (7 mL) with continuous stirring. Then a cold aqueous solution of $NaBH_4$ (5.513×10^{-2} M, 1.75 mL) was added slowly. The colour of the two solutions was immediately changed to black indicating the formation of PtNPs. Each solution was kept under stirring for another 0.5 h in ice bath and the absorbance of each solution was measured after 1 h.

RESULTS AND DISCUSSION

UV-visible spectrophotometry: Fig. 2a shows the UV-visible spectrum of a solution prepared by the addition of $NaBH_4$ (5.513×10^{-2} M) to a solution of $PtCl_6^{2-}$ (2.13×10^{-3} M) and ceftriaxone (2.68×10^{-3} M). The final concentrations of reactants were (5.55×10^{-3}, 1.997×10^{-3} and 2.1588×10^{-3} M, respectively). The colour of solution was turned to pale brown and the spectrum showed that the peak related to $PtCl_6^{2-}$ remained in its position at 260 nm, indicating weak or no reduction of $PtCl_6^{2-}$ took place by ceftriaxone. The same result was obtained when sodium borohydride was added to a solution of $PtCl_6^{2-}$, trisodium citrate and ceftriaxone, so that the final concentrations were (5.55×10^{-3}, 1.997×10^{-3}, 1.083×10^{-3} and 1.079×10^{-3} M, respectively) as is shown in Fig. 2b. These results indicate that the addition of ceftriaxone to $PtCl_6^{2-}$ leads mainly to the formation of a stable Pt(IV) complex which cannot be reduced by sodium borohydride under the specified conditions in presence or absence of trisodium citrate.

When a solution of $NaBH_4$ (5.513×10^{-2} M) was added to $PtCl_6^{2-}$ (2.13×10^{-2} M) in presence of trisodium citrate (2.695×10^{-3} M), the colour of solution changed to black immediately and the spectrum exhibited the absence of the absorption band related to $PtCl_6^{2-}$ ions which indicate the formation of PtNPs. When a solution of ceftriaxone (2.68×10^{-3} M) was added, the black colour of the colloid remained unchanged and the peak related to ceftriaxone was shifted to shorter wavelengths and appeared 220 nm. Fig. 3 shows the absorption spectrum of PtNPs after the addition of ceftriaxone (2.68×10^{-3} M). The

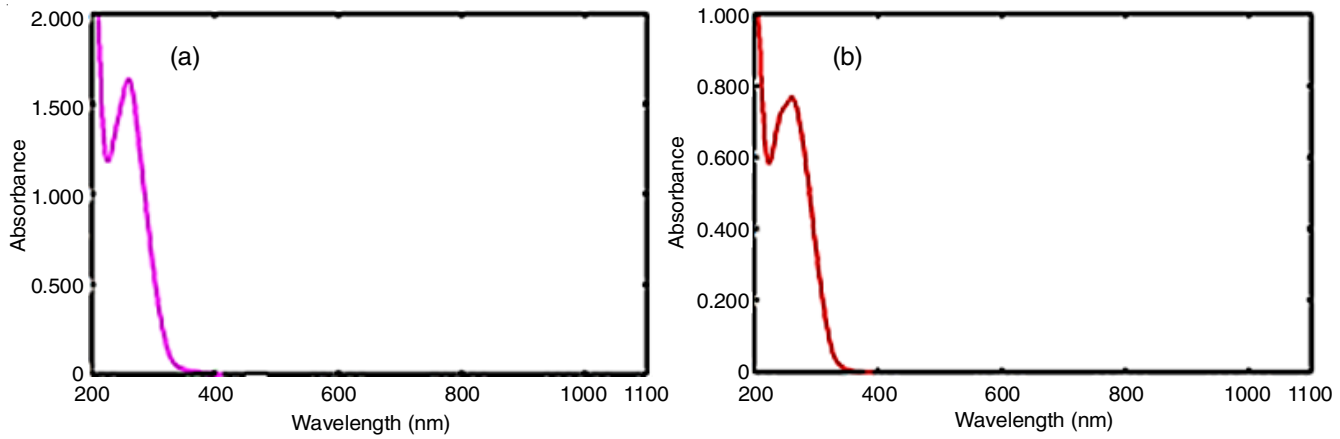


Fig. 2. Absorption spectra of two aqueous solutions prepared by addtion of $NaBH_4$ (5.55×10^{-3} M) to a solution of (a) $PtCl_6^{2-}$ (1.997×10^{-3} M) in presence of ceftriaxone (2.1588×10^{-3} M); (b) $PtCl_6^{2-}$ in presence of trisodium citrate and ceftriaxone (1.997×10^{-3}, 1.085×10^{-3} and 1.079×10^{-3} M, respectively)

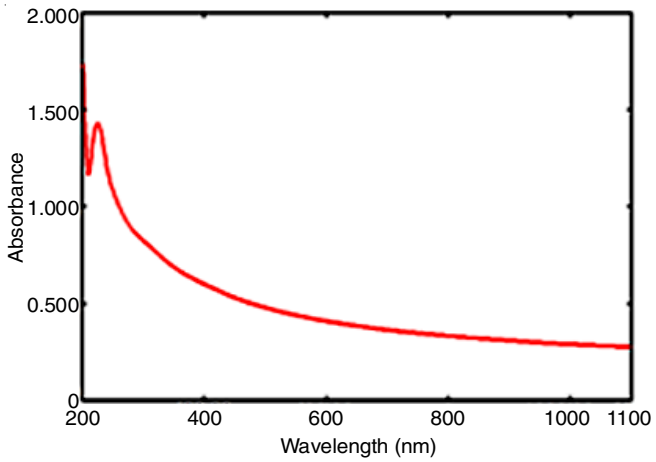


Fig. 3. Absorption spectrum of PtNPs prepared by reducing $PtCl_6^{2-}$ with $NaBH_4$ in presence of trisodium citrate followed by the addition of ceftriaxone (1.997×10^{-3}, 5.55×10^{-3}, 1.085×10^{-3} and 1.079×10^{-3} M, respectively)

final concentrations of the reactants were (5.55×10^{-3}, 1.997×10^{-3}, 1.085×10^{-3} M and 1.079×10^{-3} M, respectively). This result indicates that the addition of antibiotic after the reduction of $PtCl_6^{2-}$ ions with $NaBH_4$ did not affect the stability of the synthesized PtNPs. Figs. 4a and 4b, show the UV-visible spectra of the L_1 ((2.62×10^{-3} M) and PtNPs that have been synthesized by addition of $NaBH_4$ (5.513×10^{-3} M) to a solution of $PtCl_6^{2-}$ (2.13×10^{-3} M), trisodiumcitrate (2.69×10^{-3} M) in presence of L_1 (2.62×10^{-3} M). The final concentrations of reactants were (5.55×10^{-3}, 1.997×10^{-3}, 1.085×10^{-3} and 1.049×10^{-3} M, respectively). The colour of solution was changed immediately to black. The spectrum exhibited the disappearance of the peak and the appearance of a maximum absorption peak near 290 nm related to PtNPs [10,11].

Figs. 5 (a and b) show the UV-visible spectra of the L_2 (2.68×10^{-3} M) and PtNPs, prepared from addition of sodium borohydride (5.513×10^{-2} M) to $PtCl_6^{2-}$ (2.13×10^{-3} M) in presence of trisodium citrate (2.69×10^{-3} M) and L_2 (2.68×10^{-3} M). The final concentrations of the reactants were (5.55×10^{-3}, 1.997×10^{-3}, 1.085×10^{-3} and 1.076×10^{-3} M, respectively). The colour of solution changed immediately to black, indicating the formation of PtNPs [10,11]. These results indicate that the two Schiff base ligands may act as both reducing and stabilizing agents in the synthesis of PtNPs and that both isatin

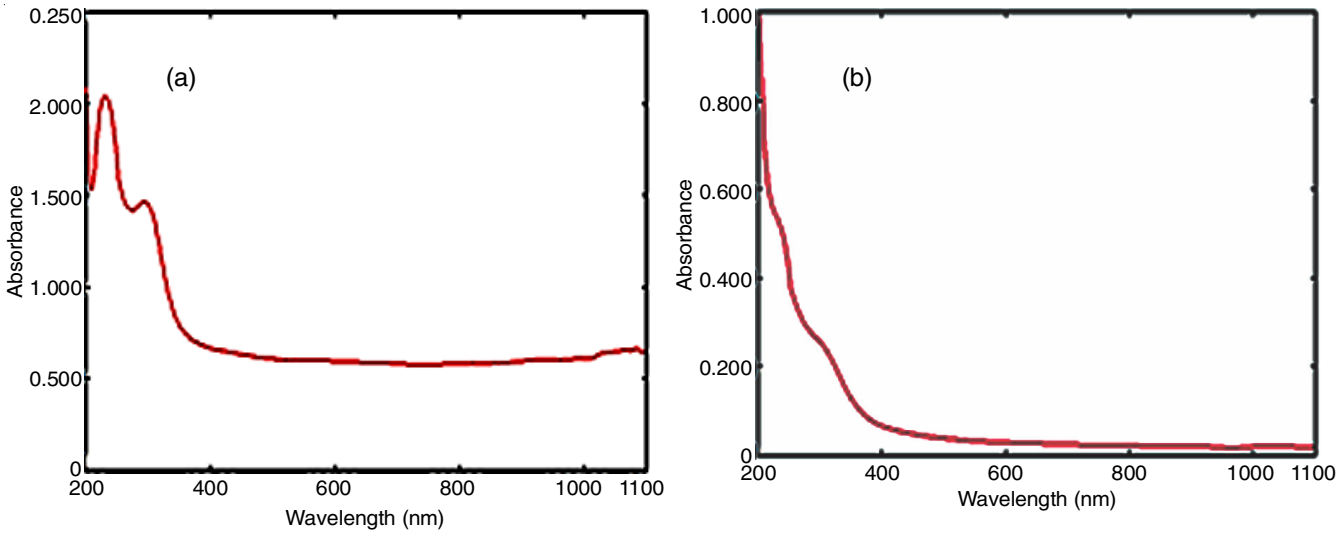


Fig. 4. (a) Absorption spectrum of L_1; (b) Absorption spectrum of PtNPs prepared from $PtCl_6^{2-}$ and $NaBH_4$ in presence of trisodium citrate and L_1 (5.55×10^{-3}, 1.997×10^{-3}, 1.085×10^{-3} and 1.049×10^{-3} M, respectively)

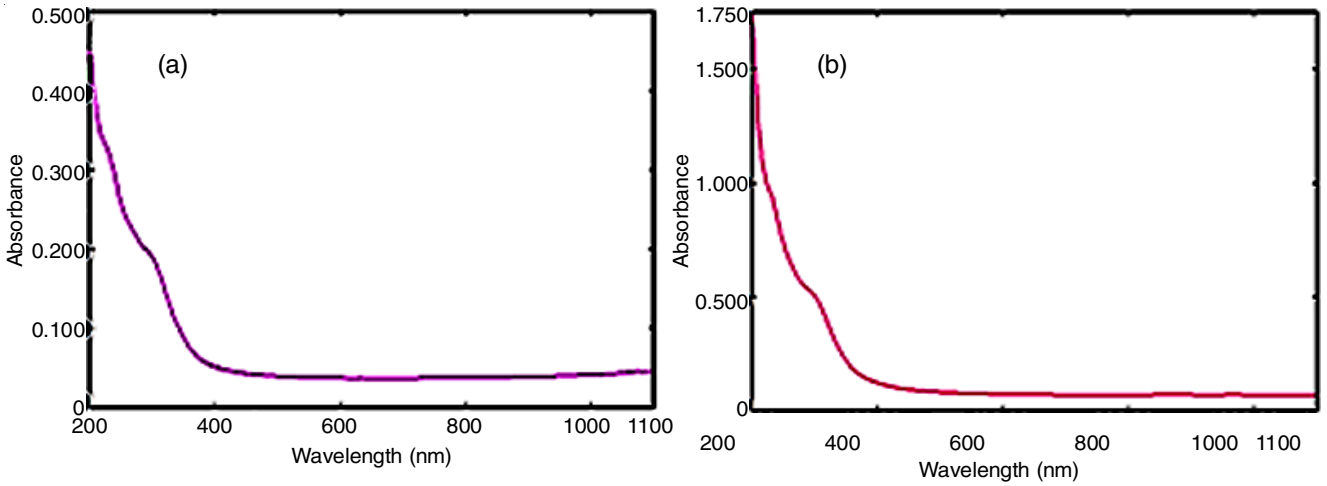


Fig. 5. (a) Absorption spectrum of L_2; (b) Absorption spectrum of PtNPs prepared from $PtCl_6^{2-}$ and $NaBH_4$ in presence of trisodium citrate and L_2 (5.548×10^{-3}, 1.997×10^{-3}, 1.085×10^{-3} and 1.076×10^{-3} M, respectivecly)

and N-acetyl isatin moieties of the two ligands, respectively enhanced the reduction process compared with the free antibiotic.

FT-IR spectra: The study of FT-IR spectra of ceftriaxone, L_1 and L_2 has been reported in previous work [9]. The bands appeared in the spectrum of ceftriaxone (Fig. 6a) which were attributed to (free NH_2 groups, N-H amide, ν(C=O) β-lactam, ν(C=O) overlapped amide and esterand $\nu_{asy}(COO^-)$ and $\nu_{sy}(COO^-)$, respectively showed decreased intensity in the spectrum of PtNPs (Fig. 6b) and their positions were shifted to (3413.77, 3282.63, 1733.80, 1610.45 and (1606.59, 1415.65 cm^{-1}), respectively.

The bands assigned to the functional groups: ν(N-H), ν(C=N), ν(C=O) (β-lactam), ν(C=O) (overlapped amide + ester), ν(COO^-) (as and sym.), ν(C=O) indole and ν(C-N) in the FTIR spectrum of L_1 (Fig. 7a) showed decreased intensities in the spectrum of PtNPs and their positions were shifted to 3172.68, 1622.02, 1748.5, 1681.81, (1660.54, 1438.80), 1675.53 and 1360.05 cm^{-1}, respectively (Fig. 7b). The bands attributed to the functional groups of L_2 (Fig. 8a): ν(C=O) of β-lactam,ν(C=N) (azomethine), ν(C=O) overlapped amide and ester, [$\nu_{asy}(COO^-)$ and $\nu_{sy}(COO^-)$] and ν(CO-CH_3) were shifted in the spectrum of PtNPs (Fig. 8b) and appeared at 1741.60,

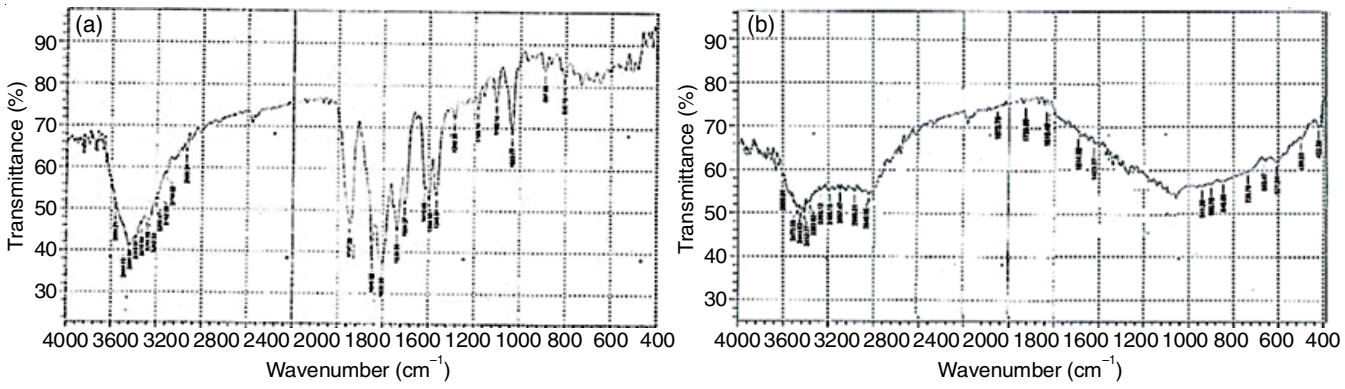


Fig. 6. FT-IR spectra of (a) ceftriaxone [9] and (b) ceftriaxone-capped PtNPs

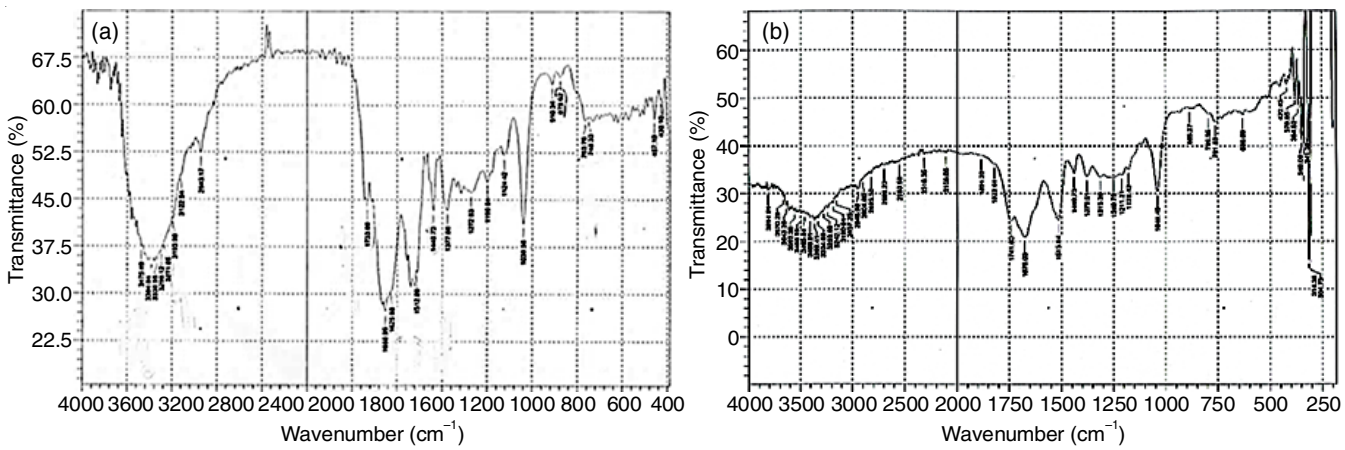


Fig. 7. FT-IR spectra of (a) L_1 [9] and (b) L_1-capped PtNPs

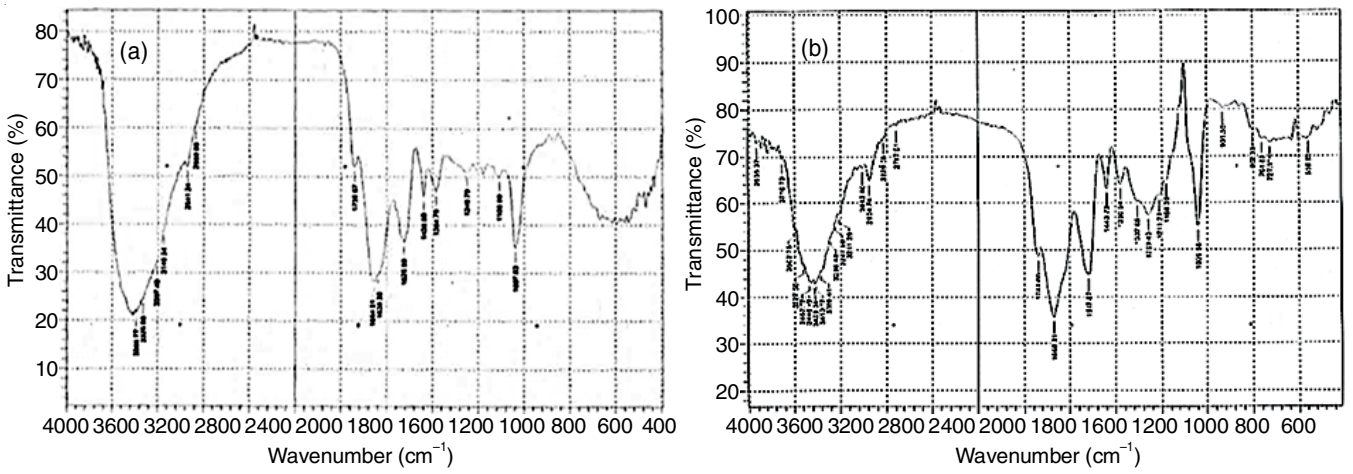


Fig. 8. FT-IR spectra of (a) L_2 [9] and (b) L_2-capped PtNPs

1668.31, 1625.10, (1517.87 and 1307.65) and 12559.34 cm^{-1}, respectively. These data indicate that the PtNPs were conjugated with the functional groups of ceftriaxone, L_1 and L_2.

X-ray diffraction (XRD): Fig. 9 shows the XRD pattern of PtNPs prepared by reduction with sodium borohydride in presence of trisodium citrate, followed by the addition of ceftriaxone. Three diffraction peaks were observed at 2θ = (39.963, 46.954 and 67.022) degree corresponding to the planes (111), (200) and (220) of face centered cubic lattice structure of PtNPs which are in agreement with the XRD pattern data available on PtNPs [1,3,12] and with those in the card number (04-0802). The crystalline sizes of nanoparticles were also estimated using Scherer's equation [13]. The average size was found nm.

Figs. 10a and 10b, show the diffraction patterns of PtNPs prepared by using sodium borohydride in presence of trisodium citrate and Schiff base ligands L_1 and L_2, respectively.

Two diffraction peaks of L_1 - capped PtNPs were observed at 2θ = (39.933° and 46.540°) corresponding to the planes (111) and (200) of face centered cubic lattice structure of PtNPs [1,3,4,12]. The XRD pattern of L_2-capped PtNPs showed three diffraction peaks observed at 2θ = (39.1980, 46.390 and 67.59) corresponding to the planes (111), (200) and (220) degree of face centered cubic Pt metal crystal lattice [1,3,12]. The

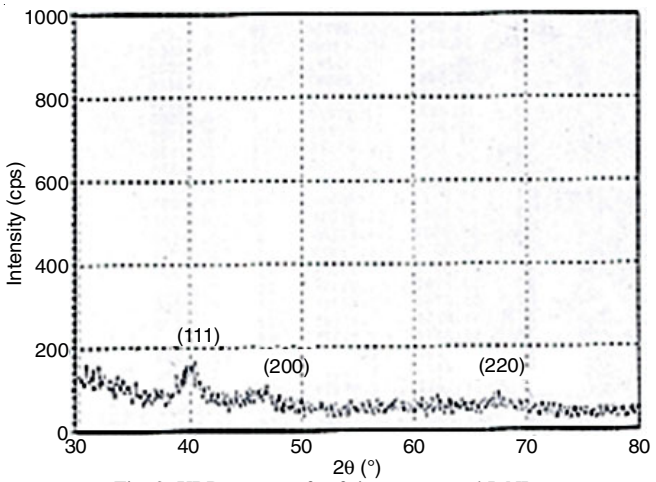


Fig. 9. XRD pattern of ceftriaxone-capped PtNPs

crystalline sizes of the nanoparticle were also estimated using unmodified Scherer's equation [13]. The average size for PtNPs conjugates of the three ligands was found 36.765, 58.39 and 42.5 nm, respectively according to the planes (111) and (200).

Scanning electron microscopy (SEM): Figs. 11 and 12 show the SEM micrographs of ceftriaxone- and L_1-capped PtNPs. The nanoparticle had nearly spherical shapes with average size 63.128 and 58.475 nm, respectively.

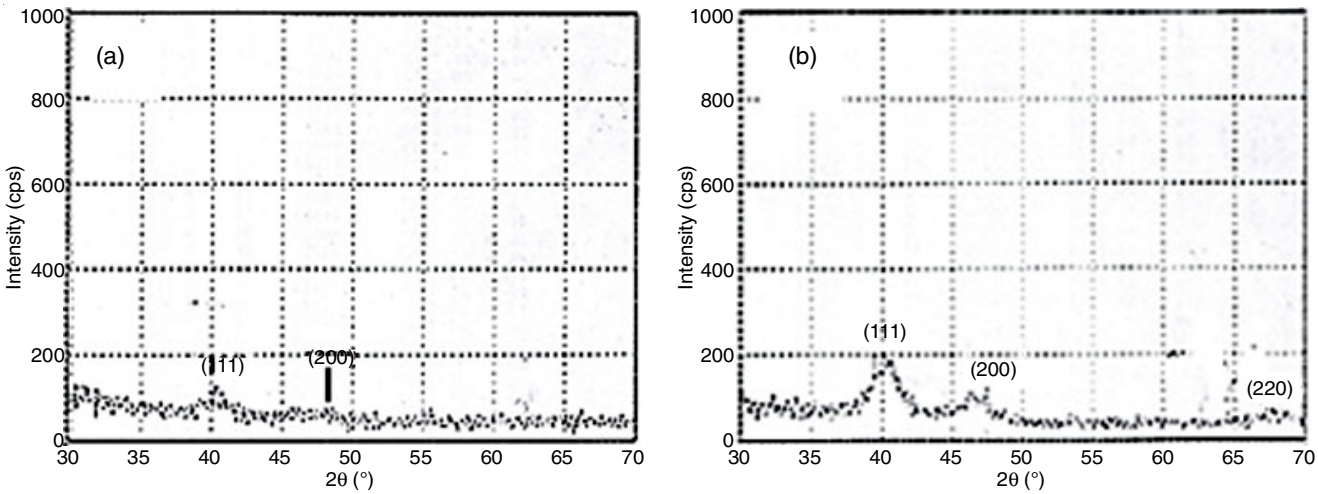


Fig. 10. XRD pattern of (a) L_1- and (b) L_2-capped PtNPs

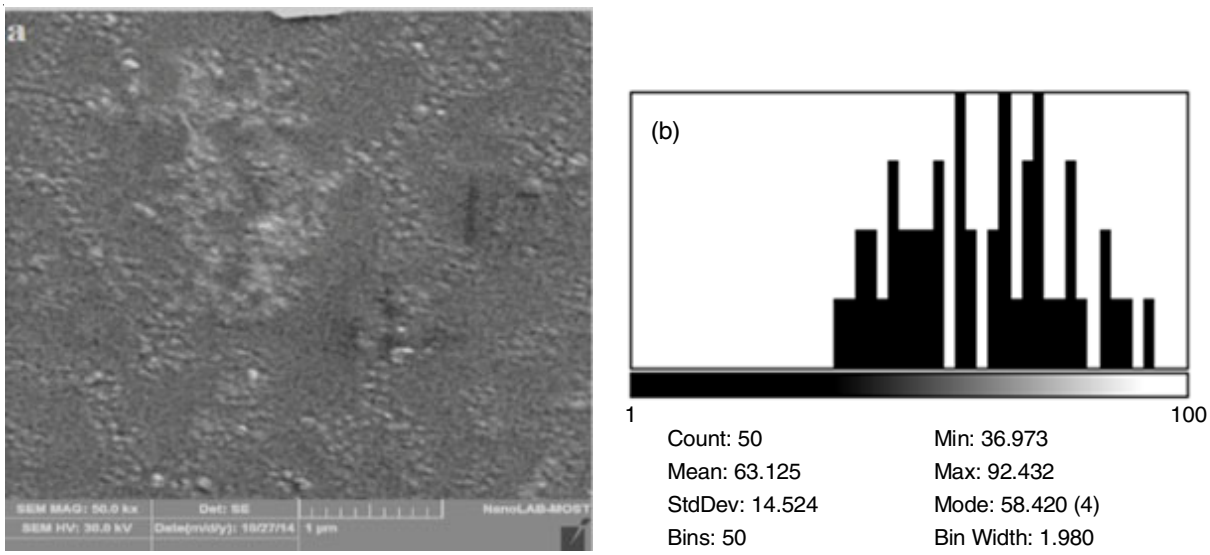


Fig. 11. (a) SEM micrograph and (b) Particle size distribution of ceftriaxone-capped PtNPs

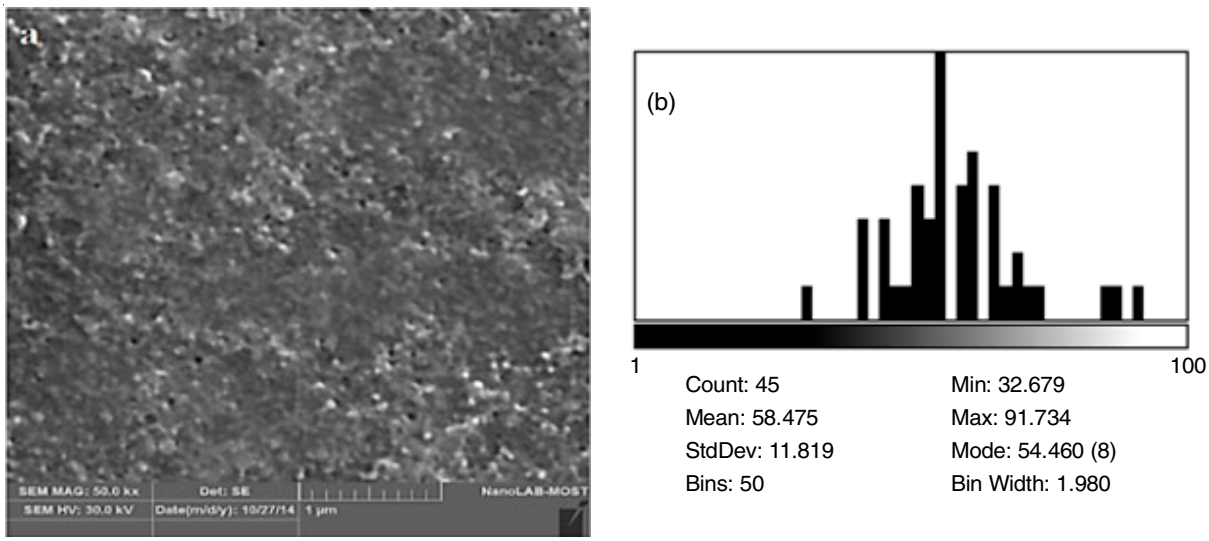


Fig. 12. (a) SEM and (b) Particle size distribution of L_1-capped PtNPs

Atomic force microscopy (AFM): The 2D and 3D AFM images and particle size diameter of as synthesized ceftriaxone-, L_1- and L_2- capped PtNPs, shown in Figs. 13-15 indicate the presence of nearly spherical PtNPs aggregates with a wide size distribution. The average sizes were 88.84, 95.12 and 83.56 nm, respectively, which are quite different from that of XRD and SEM analysis.

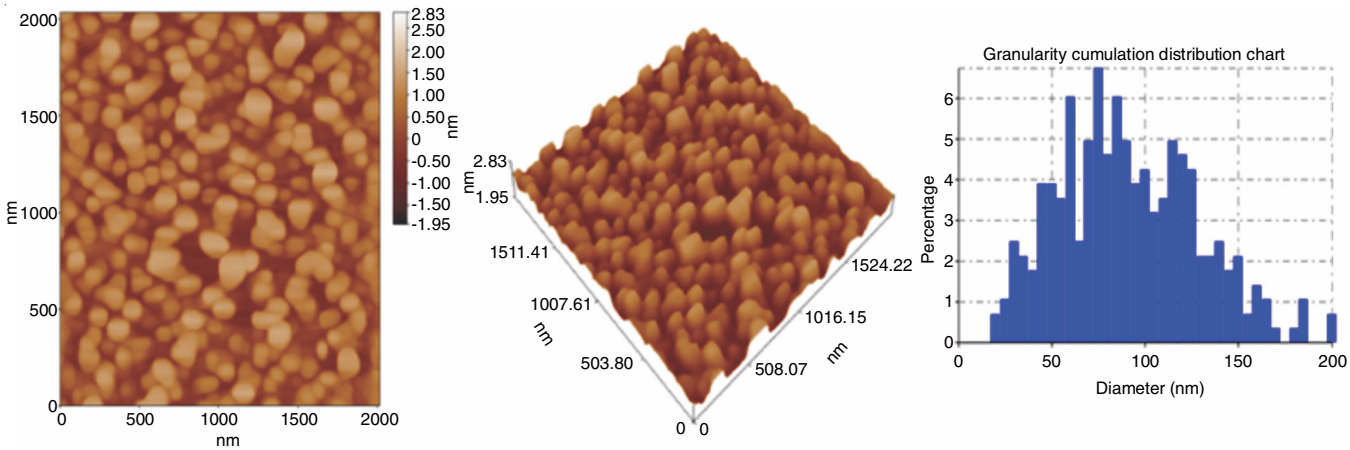


Fig. 13. AFM image and size distribution of ceftriaxone-capped PtNPs (average diameter 88.84 nm)

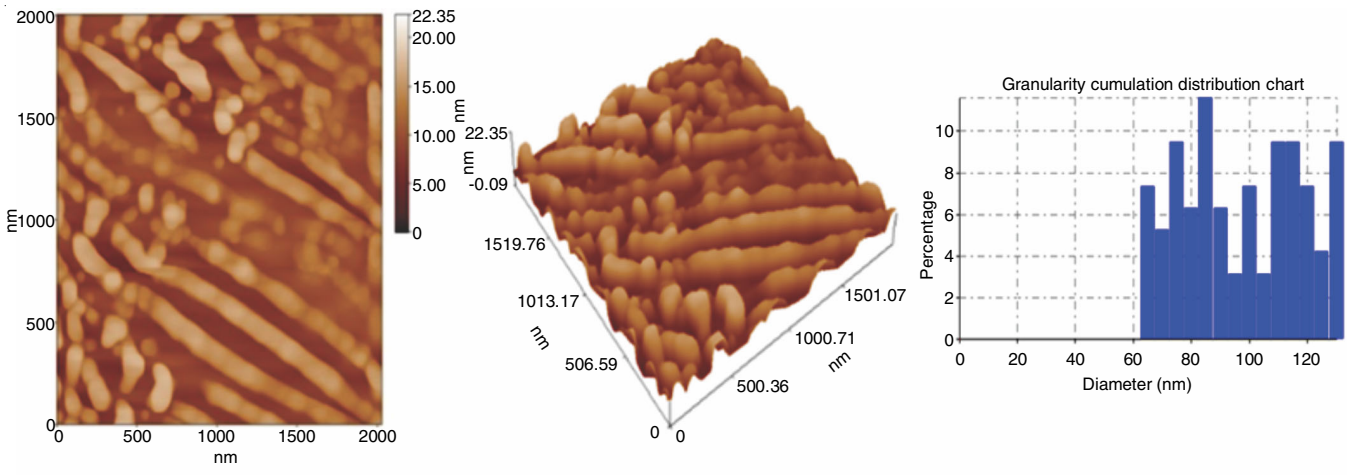


Fig. 14. AFM image and size distribution of theL_1-capped PtNPs. Average size diameter 95.12 nm

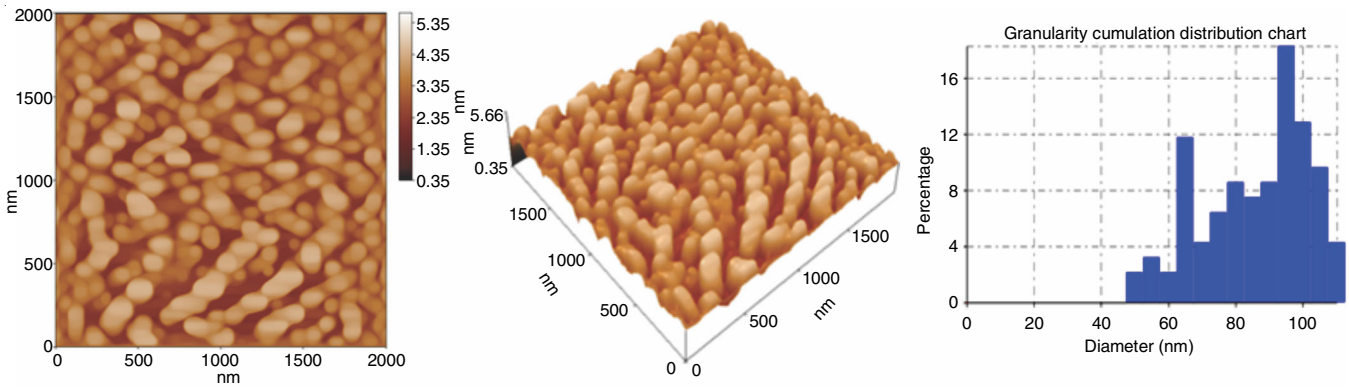


Fig. 15. AFM image and size distribution of L_2- capped (average diameter 83.56 nm)

Conclusion

Synthesis of platinum nanoparticles conjugates by reducing $PtCl_6^{2-}$ anions with $NaBH_4$ and trisodium citrate in aqueous solutions was achieved using ceftriaxone antibiotic and two of its Schiff base derivatives. No reduction took place on adding $NaBH_4$ to $PtCl_6^{2-}$ solution in presence of ceftriaxone which refers to the formation of stable platinum complex of ceftriaxone, while the reduction process took place on adding $NaBH_4$ to $PtCl_6^{2-}$ solution in presence of the two Schiff base ligands. On the other hand, adding ceftriaxone after the reduction process did not affect the stability of PtNPs. The crystal structure, sizes and morphology of the synthesized nanoparticles were characterized by XRD, SEM and AFM. Conjugation of the three ligands with PtNPs was confirmed by FT-IR spectra.

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