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Novel conducting polymer functionalized with metal–cyclam complex and its sensor application: Development of azidothymidine drug sensor

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ABSTRACT

Functionalization of polyanthranilic acid (PAA) a self-doped conducting polymer with Co(II) metal complex has been reported and is used in the development of azidothymidine drug sensor. For the first time synthesis of a new type of polymer complex of Co(II)–cyclam macrocyclic ligand (1,4,8,11-tetraazacyclotetradecane) with carboxylated polymer (as a second ligand) has been successfully accomplished and discussed in the present paper. The interaction of Co(II)–cyclam complex with polyanthranilic acid has been studied in solution phase using UV–vis spectra. Further, the formation and growth study of mixed ligand complex is carried out using electrochemical quartz crystal microbalance. The characterization of solid mixed ligand complex Co(II)–cyclam–polyanthranilic acid (Co(II)–Cy–PAA) has been carried out for its structural, thermal and electrochemical properties using various techniques viz. FT-IR, SEM, ESR, DSC, impedance and electrochemical techniques. Electrochemical study shows the potential of mixed ligand complex towards catalytic and sensor applications. The mixed ligand complex for the first time is used in the development of "azidothymidine" anti-HIV drug sensor. The analysis of azidothymidine is known over hanging drop mercury electrode using electroreduction technique, however, for the first time its analysis is reported over graphite paste electrode modified with newly synthesized mixed ligand complex. Azidothymidine is quantified in wide range of concentration with 1 μM detection limit over modified graphite paste electrode, which shows potential to develop users friendly (non-toxic and simple) gadgets and low cost screen printed electrodes.

1. Introduction

The prime objective of this work was to synthesize conjugated polymer which contains transition metal complex having central metal Co(II) ion coordinated with macrocyclic ligand (1,4,8,11-tetraaza cyclotetradecane) (Cyclam, Cy) and to explore the possibility in sensor application. Coordination compounds containing macrocyclic ligands have been intensively studied due to their wide applications in biological and sensor fields [1–6].

The incorporation of chemical or metal complexes into the conducting polymer matrixes and development of chemically modified electrodes have been one of the successful strategies in the recent years to increase the catalytic activity of the modified electrode, which enhances the electron transfer process as well as selectivity [7–13]. The possibilities of attachment of metal complexes are either through entrapment inside the polymer matrixes or linkage as pendant groups. The entrapped or physically adsorbed complexes in the polymer matrixes show poor processing and leaching properties, which are the major disadvantages. In addition, the poor electronic communication of the complex with the polymer coated electrodes also causes irreproducible results and poor sensitivity. The chemical linkage of metal complexes with the polymers can be done via coupling of suitable functional groups present over the ligand and polymer backbone. However, such reaction may affect the conductivity of the polymers or during the reaction steps polymer chains may also break.

In the present manuscript we report the development of carboxylated self-doped conducting polymer "polyanthranilic acid" (PAA) coupled with Co(II)–cyclam complex via coordination bonding through its free –COOH groups as a second ligand. Metal–Cy complexes are well known to form mixed ligand complexes (conversion from square planar or tetrahedral complex to octahedral complexes) with moderate to strong ligands [3]. Co(II)–Cy–PAA coordination complex is formed and characterized using various techniques and used for development of anti-HIV drug sensor. HIV infection is one of the major threats to human health due to the lack of relevant vaccine and drugs to cure AIDS. Acquired immunodeficiency syndrome (AIDS), caused by human immunodeficiency virus (HIV), is an immunosuppressive disease. Dideoxycytidine, dideoxyadenosine, dideoxyinosine and 3′-azido-3′-deoxythymidine drugs show antiviral activity and suppress the monocyte/macrophages in HIV infected patients [14]. Azidothymi-

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dine (AZT, Zidovudine, Retrovir, 3′-azido-3′-deoxythymidine) antiviral drug was first approved for the treatment of patients with human immunodeficiency virus (HIV) infection [15]. However, detection of this drug is very important due to its toxic effects above 10 μM serum concentrations in human [16]. The electrochemical detection of the drug is known based on hanging mercury electrodes, but this technique did not get much attention due to the toxicity of the mercury and difficulty in development of users friendly gadgets and low cost screen printed electrodes.

The modified electrode showed excellent redox and catalytic properties due to mixed nature of the Co(II)–Cy complex and conducting polymer and showed potential for development of low cost and sensitive sensor for AZT.

2. Experimental

2.1. Materials and instruments

1,4,8,11-Tetraaza cyclotetradecane and mineral oil (nujol) were purchased from Aldrich Chemicals Company, MA, USA. Cobalt chloride ($CoCl_2{\cdot}6H_2O$), graphite powder and sulfuric acid were purchased from Merck, Mumbai, India. Fresh stock solution of anti-HIV drug azidothymidine (Sigma Chemical Co. (St. Louis, MO, USA) was freshly prepared in 0.1 M Tris–HCl buffer (pH 6) and purged with pure nitrogen gas for 5 min and protected from light.

Formation of mixed ligand complex of Co(II)–Cy with PAA was studied using Electrochemical Quartz Crystal Microbalance (EQCM), Autolab, The Netherlands. Complexes were characterized using Electrochemical Workstation, CH-Instrument Inc., TX, USA, EPR spectroscopy, Bruker EMX 1444 EPR spectrometer, Germany, UV–vis spectroscopy, lambda 25 spectrophotometer of PerkinElmer, Germany and FT-IR, Thermo 5700 Germany, differential scanning calorimetry (DSC), METTLER TOLEDO, FP900 Thermosystem, Germany and using SEM, SHIMADZU SS550, Japan.

2.2. Synthesis of Co(II)–Cy and Co(II)–Cy–PAA complexes

Co(II)–Cy complex was prepared in 1:2 mole ratios of $CoCl_2$ and cyclam solution was prepared in 0.1 M Tris-buffer at pH 6 [3]. Mixture was incubated for 5 h and formation of the complex was observed by recording UV–vis spectra [3]. Co(II)–Cy complex formed in solution phase only and no solid complex was obtained as precipitation. To obtained a mixed ligand complex, PAA solution was added to the Co(II)–cyclam solution (preincubated for 2 h) in mole ratio of 1:2:10. Immediately after mixing the solutions, solid mass appeared and settled down at bottom. The solution was allowed to incubate for 4–5 h at room temperature followed by filtration. Solid complex was washed properly and dried under vacuum at room temperature.

2.3. Preparation of modified electrodes

Co(II)–Cy–PAA complex modified electrodes were prepared either by modifying surface of the carbon paste electrode or forming the mixed ligand complex directly over the Pt electrode coated with PAA followed by incubation in Co(II)–Cy complex solution for 4–5 h.

3. Results and discussion

UV–vis spectrum of $CoCl_2$ taken in 0.1 M Tris–HCl buffer (pH 6) showed three peaks at 511, 468 and 256 nm [17], while spectrum for Co(II)–Cy complex in 0.1 M Tris–HCl buffer (pH 6) showed absence of Co(II) peaks and a new peak at 455 nm was appeared along with a weak shoulder at 537 nm as shown in Fig. 1 curves A and B, respectively. This new peak at 455 nm was attributed to the formation of Co(II)–Cy during the incubation of metal ions and cyclam. UV–vis spectrum of PAA showed three characteristic peaks at 545, 341 and 271 nm (cf. Fig. 1curve C) [18], while after mixed ligand complex formation with Co(II)–Cy complex, peaks appeared at 527 and 365 nm, which indicated the formation of a new complex [19].

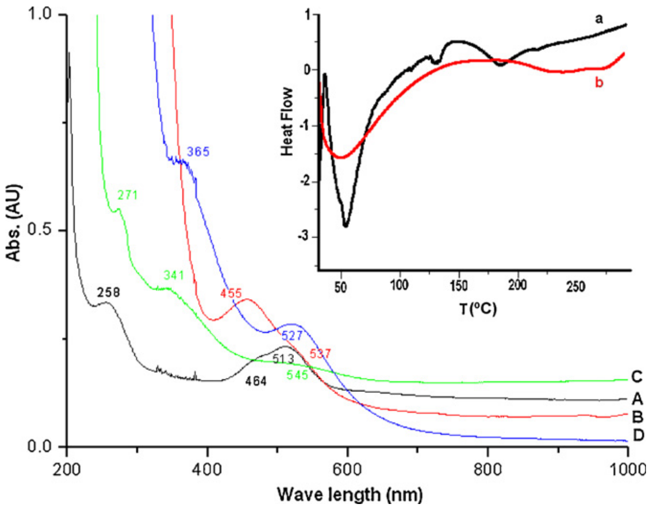


Fig. 1. UV–vis spectra of (A) $CoCl_2{\cdot}6H_2O$, (B) Co(II)–Cy, (C) PAA and (D) Co(II)–Cy–PAA. Inset: DSC of (a) PAA and (b) Co(II)–Cy–PAA in 0.1 M Tris–HCl buffer (pH 6).

The formation of Co(II)–Cy mixed ligand complex was also supported by DSC study as shown in Fig. 1(inset). The DSC data showed three major endothermic peaks for pure PAA at 55 °C due to water loss and 130 and 180 °C due to loss of alternate –COOH and all the –COOH groups, respectively [20]. However, after complex formation with Co(II)–Cy the second and third exothermic peaks due to loss of –COOH shifted towards higher temperature as 235 and 280 °C (cf. inset Fig. 1curve b). The higher temperature shift of decomposition temperature indicated stability of –COOH group probably due to interaction with Co(II)–Cy complex to form a mixed ligand octahedral complex.

Further the FT-IR studies also supported the formation of mixed ligand complex. Cyclam shows characteristic peaks at 1070, 2872 and 3422 cm^{-1} corresponding to C–N, C–H, N–H (figure not shown) [3], while PAA showed characteristic peaks at 1511 and 1571 cm^{-1} due to stretching of benzenoid and quinoid rings, 1692 cm^{-1} for (C=O) carbonyl group, 835 cm^{-1} due to C–H deformation of trisubstituted benzene and a broad hump around 3200 cm^{-1} due to –OH stretching (cf. Fig. 2curve a). Cy and PAA both showed its presence in Co(II)–Cy–PAA complex as 1499 and 1577 cm^{-1} peaks appeared due to stretching of benzenoid and quinoid rings, while peaks at 1059 and 3422 correspond to C–N, N–H of Cy [18]. A shift in C–N cyclam was observed due to coordination of Co(II) ions with cyclam ring. The O–H stretching of PAA diminished and C=O stretching considerably shifted to1652 cm^{-1} probably due to coordination of –COO group with Co(II)–Cy as shown in Fig. 2curve b.

Electrochemical studies were carried out for cyclam, $CoCl_2$, Co(II)–Cy, and Co(II)–Cy–PAA complexes in 0.5 M H_2SO_4 using differential pulse voltammetry. The acidic pH was maintained in order to retain the electroactivity of PAA. Anodic differential pulse voltammetry of $CoCl_2$ showed two peaks at −0.09 V (due to Co(I)/Co(II)) and 0.98 V (due to Co(II)/Co(III)) vs. Ag/AgCl as shown in Fig. 3. Co(II)–Cy complex again showed two peaks due to redox reaction of Co(II) central ion as on −0.25 and 1.00 V vs. Ag/AgCl. However, Co(I)/Co(II) oxidation shifted towards lower potential probably due to complex formation (pushing of electron density of

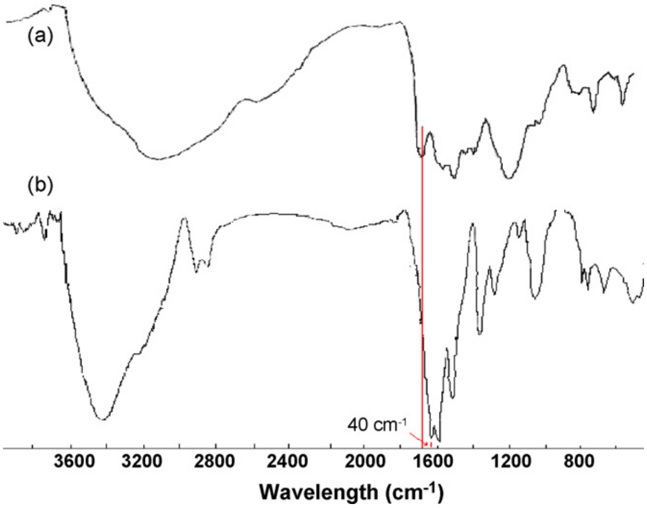


Fig. 2. FT-IR spectra of (a) PAA and (b) Co(II)–Cy complex with PAA.

ligand towards Co(II) ions). Polyanthranilic acid showed four oxidation peaks as 0.04, 0.149, 0.55 and 0.82 V vs. Ag/AgCl as shown in Fig. 3. After mixed ligand complex formation all the characteristic oxidation peaks of Co(II)–Cy as well as PAA were appeared as shown in Fig. 3. However, there were some minor shifts observed after complex formation. In Co(II)–Cy–PAA complex conversion of Co(II) to Co(III) was observed at 1.0 V, which showed the presence of one unpaired electron in the Co(II) d orbital. The presence of unpaired electron is also supported by EPR spectra as *g*-value 2.20 indicates low spin Co(II) complex [21–23]. The presence of one unpaired electron as evidence of low spin complex showed the octahedral nature of the mixed ligand complex. Above characterization supported that Co(II)–Cy transformed from square planer to octahedral complex after addition of second ligand as PAA. Electrochemical impedance spectroscopy also supported the functionalization of PAA with Co(II)–Cy complex as the R_{ct} (charge transfer resistance) value significantly increased after modification of conducting polymer with Co(II)–Cy as shown in inset of Fig. 3.

Scanning electron microscopy technique is used to study the morphological change in polymer before and after modification with metal complex. The microstructure of polyanthranilic acid showed quite compact structure with smaller grains (cf. Fig. 4a), however, after functionalization with metal–cyclam complex the microstructure changed and converted to homogenous solid flacks as shown in Fig. 4b. Probably the interaction of Co(II)–Cy complex with the polymer chains caused the significant change in the morphology.

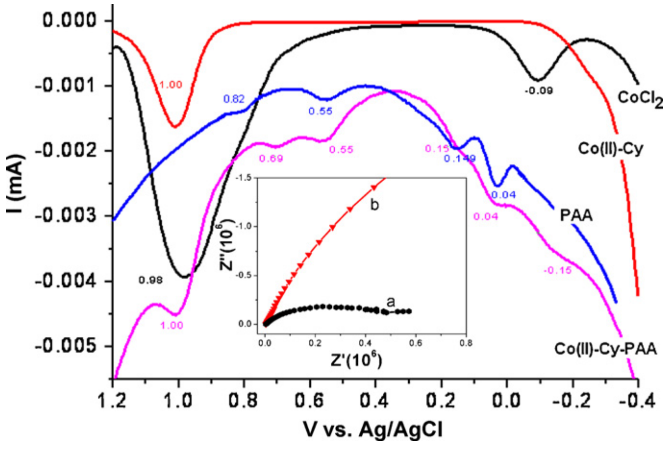


Fig. 3. Differential pulse voltammetric of $CoCl_2$, Co(II)–Cy, PAA and Co(II)–Cy–PAA in 0.5 M H_2SO_4. Inset: Nyquist plot of (a) PAA and (b) Co(II)–Cy–PAA in same electrolyte.

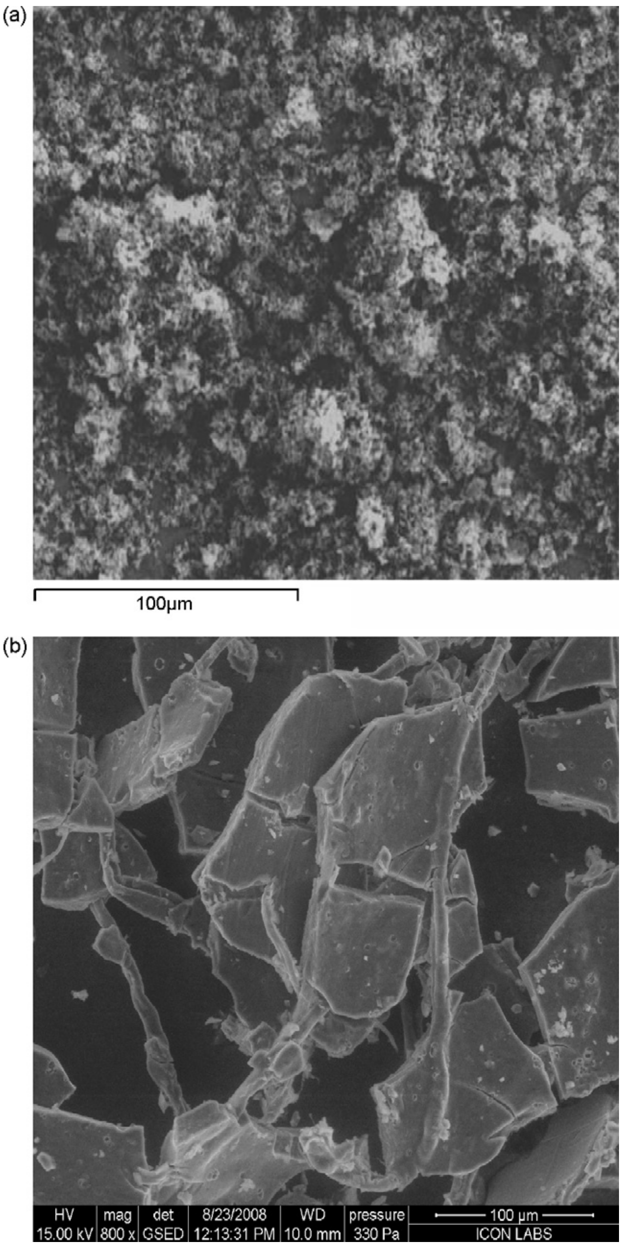


Fig. 4. SEM images of (a) PAA and (b) Co(II)–Cy–PAA.

The interaction of Co(II)–Cy with PAA and formation of mixed ligand complex was also studied by Electrochemical Quartz Crystal Microbalance (EQCM) [24]. EQCM study showed the formation of polymer complex. The gold coated quartz crystal (5 MHz) electrode was used for the study. Polyanthranilic acid was coated over the gold electrode and dipped in the Co(II)–Cy solution for formation of mixed ligand complex with PAA and rate of formation was observed using EQCM.

First the blank mass of bare crystal in air was taken as 0.00 $\mu g/cm^2$ as shown in block A of Fig. 5a. Polyanthranilic acid was coated over gold crystal by solution casting technique from its THF solution and variation of mass of the crystal was recorded as shown in block B of Fig. 5a. After deposition of PAA and evaporation of the solvent the PAA coated gold quartz crystal was dipped into Tris–HCl buffer (pH 6) as shown in block C of Fig. 5a. The PAA coated crystal mass was found to be 53.029 $\mu g/cm^2$, which indicated the mass of

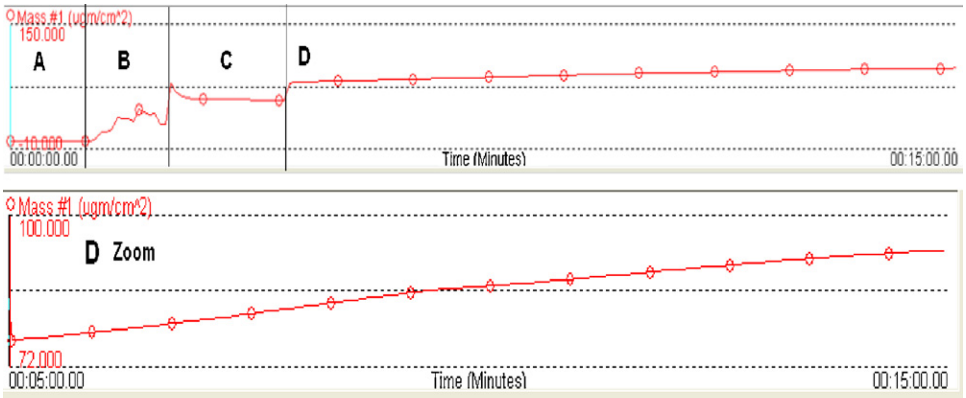


Fig. 5. EQCM data showing change in mass of the crystal (coated with PAA) vs. time due to complex formation between PAA with Co(II)–Cy solution in 0.5 M H_2SO_4.

PAA film coated over gold crystal as shown in block C of Fig. 5a. After 5 min, solution of Co(II)–Cy for 2 h was added to the buffer solution and change in mass was observed for further 10 min time period as shown in block D of Fig. 5a and its zoom of Fig. 5b. After 10 min, the total change in mass was observed as 22.351 $\mu g/cm^2$ (75.380–53.029 $\mu g/cm^2$), which indicated mixed ligand complex formation of Co(II)–Cy–PAA. The coated crystal was washed and further mass was calculated which showed negligible decrease in the total mass.

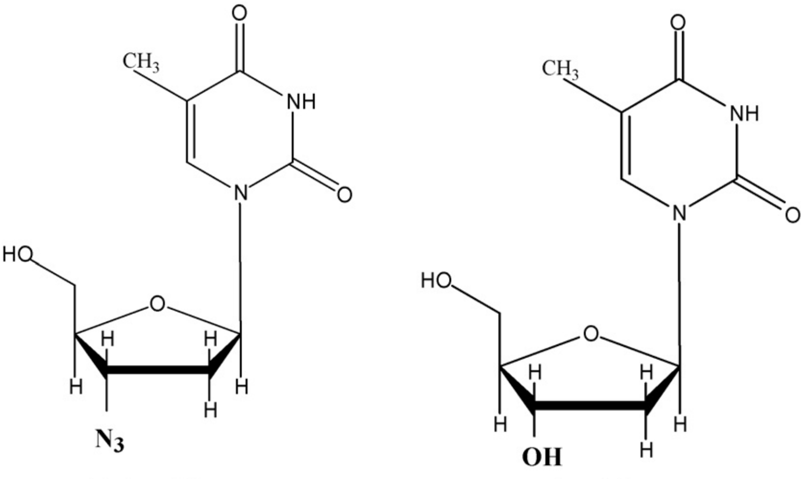
3.1. *Electro-reduction studies of azidothymidine*

After successful development of electroactive and stable Co(II)–Cy–PAA mixed ligand complex, modified electrodes are developed either modifying the PAA coated Pt electrodes with Co(II)–Cy complex or incorporating solid mixed ligand complex in graphite paste and filling in glass capillaries of 0.5 mm diameter [2]. The modified electrodes were used for trace estimation of anti-HIV drug (AZT) based on following common electro-reduction mechanism of azido group [16]:

$$RN_3 \xrightarrow{[H]} NR{=}NH_2 \rightarrow RNH_2 + N_3$$

Fig. 6 shows the structure of AZT and its parent compound, thymidine. The difference between these two compounds is the substitution of an azido group for a hydroxyl group on the sugar ring of the nucleic acid. The azido group is responsible for the in vivo action of AZT as an antiviral agent [16,25]. The reduction of this azido group was the basis for the electrochemical analysis of this drug [26,27].

AZT electro-reduction was tried to carry out over bare electrode (without modified electrode) in 1 mM Tris–HCl (pH 6), however, low micromolar concentrations did not give any reduction peak. Reduction peak appeared for 1 mM concentration of AZT at 0.1 V vs. Ag/AgCl as shown in Fig. 7a. PAA reduction reaction was also recorded in 1 mM Tris–HCl (pH 6) by coating the electrode with PAA as shown in Fig. 7b, which showed three well resolved peaks at −0.19, 0.04 and 0.40 V vs. Ag/AgCl. When the 50 μM concentrations of AZT was added in the electrolyte and electro-reduction was carried out over PAA modified electrode neither any increase in the peak height of PAA nor appearance of any new peak was observed as shown in Fig. 7c. In fact the second and third peaks of PAA (from lower potential) decreased after addition of micromolar concentration of AZT. Finally the electrode was modified with Co(II)–Cy–PAA complex and electro-reduction was carried out in 1 mM Tris–HCl (pH 6), it showed two-week humps at −0.01 and 0.36 V vs. Ag/AgCl as shown in Fig. 7d. When a 5 μM concentration of AZT was added in the same electrolyte and electro-reduction was carried out over Co(II)–Cy–PAA modified electrode, it showed two broad peaks one at 0.08 V and another at 0.42 V vs. Ag/AgCl as shown in Fig. 7e. A small shift in the reduction of AZT over Co(II)–Cy–PAA modified electrode was observed in comparison to bare electrode. Both the AZT reduction peaks showed significant increase in the peak current when the increasing concentration of AZT was added to the



Azidothymidine Thymidine

Fig. 6. Structure of AZT and its parent compound “thymidine”.

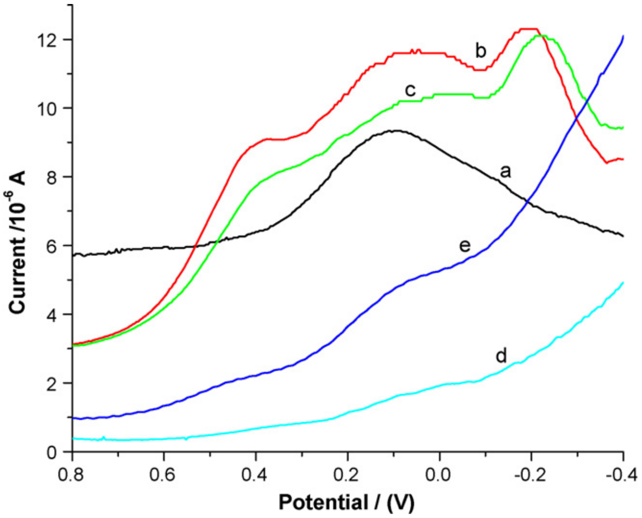


Fig. 7. Electro-reduction using differential pulse voltammetry (pulse amplitude 0.05 V) in 1 mM Tris–HCl (pH 6) of (a) 1 mM AZT over graphite paste electrode, (b) PAA alone coated over graphite paste electrode, (c) PAA in the presence of 50 μM AZT, (d) Co(II)–Cy–PAA mixed ligand complex alone and (e) 5 μM AZT over the Co(II)–Cy–PAA modified graphite paste electrode.

electrolyte as shown in Fig. 8. However, a small peak shift towards negative potential was observed for higher concentrations of AZT, which was significant for 50 μM. The AZT reduction peak current (peak at 0.08 V vs. Ag/AgCl) showed a linear increment in peak current with the concentration of AZT drug when the log current vs. log concentration was plotted. However, such linear relation was not observed for the second peak appeared at 0.42 V vs. Ag/AgCl. The reduction of AZT drug from 1 to 100 μM concentration was carried out over Co(II)–Cy–PAA modified electrode and calibration curve between log peak current vs. log AZT concentration was plotted as shown in Fig. 9. Wide concentration range linearity was observed with detection level of 1 μM AZT concentration. Sensor showed reproducibility within 5% range for several sets of readings.

Further this technique was validated with spectrophotometric method, which is a well known and most common method for clinical analysis of this drug [28]. Spectrophotometric technique is having detection limit of 20 μM AZT concentration [28], so we compared both the techniques for a sample of 25 μM AZT concentration

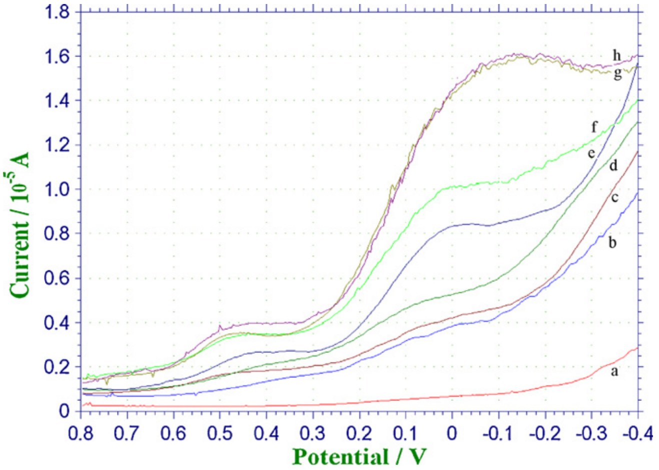


Fig. 8. Differential pulse voltammetry (pulse amplitude 0.05 V) of AZT over Co(II)–Cy–PAA modified electrode for various concentrations from (b) 0 μM, (c) 1 μM, (d) 5 μM, (e) 10 μM, (f) 25 μM, (g) 50 μM and (h) 100 μM in 1 mM Tris–HCl (pH 6). (a) Response of bare graphite paste electrode in same solution.

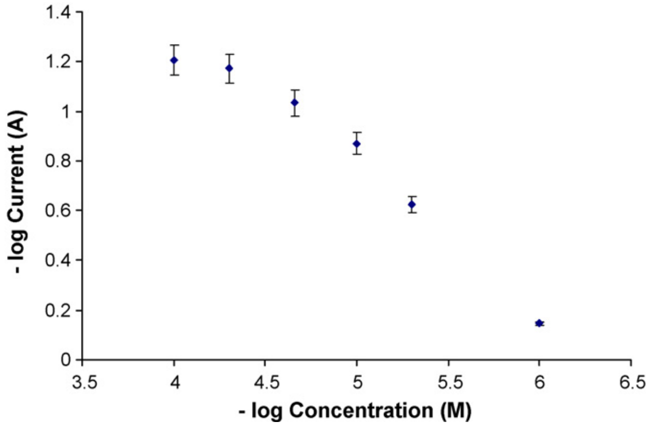


Fig. 9. Calibration plot for AZT estimation carried out using differential pulse voltammetry as shown in Fig. 8.

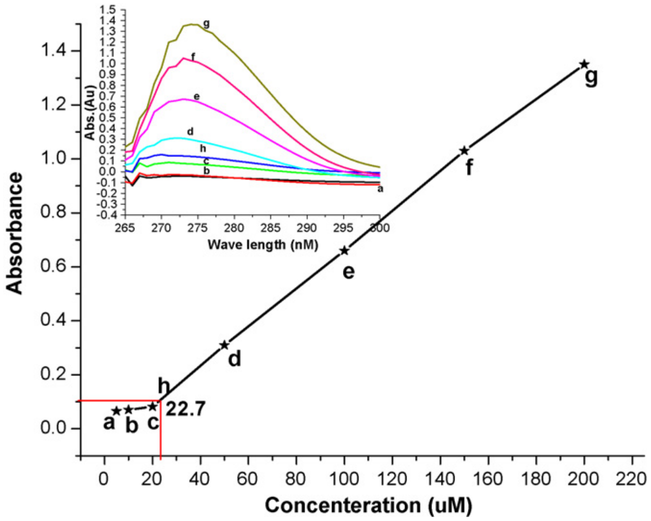


Fig. 10. Calibration plot for AZT estimation carried out using spectrophotometric technique and estimation of unknown concentration sample. Inset: UV–vis spectrum of AZT for various concentrations from (a) 5 μM, (b) 10 μM, (c) 20 μM, (d) 50 μM, (e) 100 μM, (f) 150 μM, (g) 200 μM and (h) as unknown concentration sample in 1 mM Tris–HCl (pH 6).

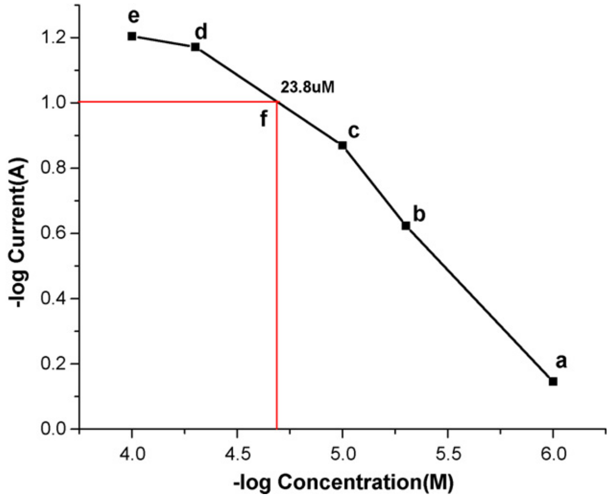


Fig. 11. Calibration plot for AZT estimation carried out using differential pulse voltammetric technique for various concentrations from (a) 1 μM, (b) 5 μM, (c) 10 μM, (d) 50 μM, (e) 100 μM and (f) as unknown concentration sample in 1 mM Tris–HCl (pH 6).

treating as unknown concentration sample. Two calibration plots were made with standard samples of AZT from 5 to 200 μM using spectrophotometric as well as our voltammetric techniques. Further the sample of 25 μM AZT was run as unknown sample for both the techniques and its concentration was calculated following standard addition method [29,30] using calibration plots as shown in Figs. 10 and 11. The spectrophotometric technique showed the concentration of unknown sample as 22.7 μM as shown in Fig. 10 and our voltammetric technique showed 23.8 μM as shown in Fig. 11. It was found that both the techniques showed quite close results within the error of 10%. However, our technique was more sensitive and precise over spectrophotometric technique.

4. Conclusion

Successful synthesis of a new type of conducting polymer-metal mixed ligand complex having Co(II)–cyclam moieties associated with polymer chain was discussed. Carboxyl group of polyanthranilic acid coordinated with Co(II)–cyclam complex and formation of octahedral low spin mixed ligand complex was supported by various characterizations tools. Further mixed ligand complex was explored for catalytic and sensor applications. Polymer complex modified electrodes were developed and used for quantification of AZT (anti-HIV drug) in aqueous samples. AZT electro-reduction was recorded over complex modified electrodes and a sensitive sensor developed for the detection in wide range of concentration from 1 to 50 μM. Further our new technique was validated with the well known spectrophotometric technique for the detection of AZT. It was found that our technique was more sensitive and precise over spectrophotometric technique.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.talanta.2009.12.023.

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