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Short Communication

Electrochemical behavior of paclitaxel and its determination at glassy carbon electrode

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ABSTRACT

The electrochemical behavior of paclitaxel drug was studied at a glassy carbon electrode in phosphate buffer solutions using cyclic and differential-pulse voltammetric techniques. The oxidation process was shown to be irreversible over the pH range (3.0–10.4) and was diffusion controlled. Effects of anodic peak potential (E_p), anodic peak current (I_{pa}), scan rate, pH, heterogeneous rate constant (k^0), etc have been discussed. A possible electro-oxidation mechanism was proposed. An analytical method was developed for the determination of paclitaxel in phosphate buffer solution at pH = 7.0 as a supporting electrolyte. The anodic peak current varied linearly with paclitaxel concentration in the range 1.0×10^{-6} M to 1.0×10^{-5} M with a limit of detection (LOD) of 1.23×10^{-8} M and limit of quantification (LOQ) of 4.10×10^{-8} M. The proposed method was successfully applied to the determination of paclitaxel in pure and real samples.

1. Introduction

Drug analysis is one of the important tools for drug quality control. Therefore, the development of a simple, sensitive, rapid, and reliable method for the determination of drugs is of great importance. Paclitaxel (PAC), chemical structure as given in Scheme 1, is a mitotic inhibitor used in cancer chemotherapy. Paclitaxel is one of several cytoskeletal drugs that target tubulin. Paclitaxel-treated cells have defects in mitotic spindle assembly, chromosome segregation, and cell division. Unlike other tubulin-targeting drugs such as colchicine that inhibit microtubule assembly, paclitaxel stabilizes the microtubule polymer and protects it from disassembly. Chromosomes are thus unable to achieve a metaphase spindle configuration. This blocks progression of mitosis, and prolonged activation of the mitotic checkpoint triggers apoptosis or reversion to the G-phase of the cell cycle without cell division [1,2].

Paclitaxel is approved for ovarian, breast and lung cancers and Kaposi's sarcoma [3]. It is recommended in NICE guidance

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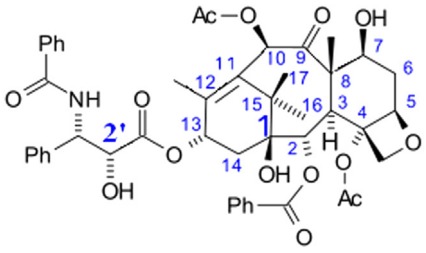


Scheme 1 – Chemical structure of paclitaxel.

of June 2001 that it should be used for nonsmall cell lung cancer in patients unsuitable for curative treatment, and in first-line and second-line treatment of ovarian cancer and it should be available for the treatment of advanced breast cancer after the failure of anthracyclic chemotherapy.

Different methods have been reported for the determination of paclitaxel, including square wave voltammetry at Cysteamine/DNA/SWNTs-Film modified Au electrode [4], liquid chromatography with anodic amperometric detection [5] and different HPLC methods for the determination of PAC [6–10]. The main problems encountered in using such methods are constructions of electrodes, time consuming extraction and separation procedures.

The present study was to develop a simple, low-cost direct current voltammetric method for determination of paclitaxel. In the present work, we carried out the electrochemical oxidation of paclitaxel at glassy carbon electrode. We optimized all the experimental parameters for the determination of paclitaxel and developed an electro analytical method for its determination. This method has the advantages such as fast response, easy repair, renewal of the paclitaxel, good reproducibility and low detection limit. The proposed method was applied to the determination of paclitaxel in the injection and urine samples.

2. Materials and methods

2.1. Materials and reagents

Pure PAC in powdered form was obtained as a gift sample from Reddy's Laboratory, Hyderabad, India and was used without further purification. A stock solution (1.0×10^{-4} M) of PAC was prepared in methanol. Paclitaxel containing injections marketed by NEON Lab. LTD. were purchased from the local pharmacy. Phosphate buffer solutions (ionic strength = 0.2 M) were prepared according to the literature method [11]. All other reagents used were of analytical grade. All solutions were prepared in millipore water.

2.2. Apparatus

The electrochemical experiments were performed with CH Instruments, USA, (Model 630D) Electrochemical Analyzer and were carried out in a 10 mL single compartment three-electrodes glass cell with a 3 mm diameter glassy carbon electrode (GCE) as the working electrode (Part No. CHI104), a platinum wire as counter electrode, and Ag/AgCl (3.0 M KCl) electrode as reference electrode. All experiments were carried out at an ambient temperature of 25 ± 0.1 °C. The pH measurements were made with Elico pH meter model LI120. The experimental conditions for differential pulse voltammetry (DPV) were: initial E: 0.8 V, final E: 1.4 V, sensitivity: 0.5 μA/V, pulse amplitude: 4 mV, sample width: 20 ms, pulse width: 0.2 s, pulse period: 500 ms.

2.3. Area of the electrode

The area of the electrode was obtained by the cyclic voltammetric method using 1.0 mM $K_3Fe(CN)_6$ as a probe at different scan rates. For a reversible process, the following Randles–Sevcik formula was used [12].

$$I_{pa} = 0.4463\left(F^3/RT\right)^{1/2} n^{3/2} A_0 D_o^{1/2} C_0 \upsilon^{1/2} \quad (1)$$

where I_{pa} refers to the anodic peak current, n is the number of electrons transferred, A_0 is the surface area of the electrode, D_0 is diffusion coefficient, υ is the scan rate, and C_0 is the concentration, respectively, of $K_3Fe(CN)_6$. For 1.0 mM $K_3Fe(CN)_6$ in 0.1 M KCl electrolyte, $T = 298$ K, $R = 8.314$ J/K.mol, $F = 96{,}480$ C/mol, $n = 1$, $D_0 = 7.6 \times 10^{-6}$ cm^2/s, then from the slope of the plot of I_{pa} vs $\upsilon^{1/2}$ the electroactive area was calculated. In our experiment the slope was 3.44×10^{-6} μA $(V/s)^{1/2}$ and the area of electrode was calculated to be 0.0464 cm^2.

2.4. Procedure

The GCE was polished using 0.3 micron Al_2O_3 before each experiment. After polishing, the electrode was rinsed thoroughly with methanol and millipore water. After this mechanical treatment, the GCE was placed in pH = 7 (0.2 M) phosphate buffer solution and various voltammograms were recorded.

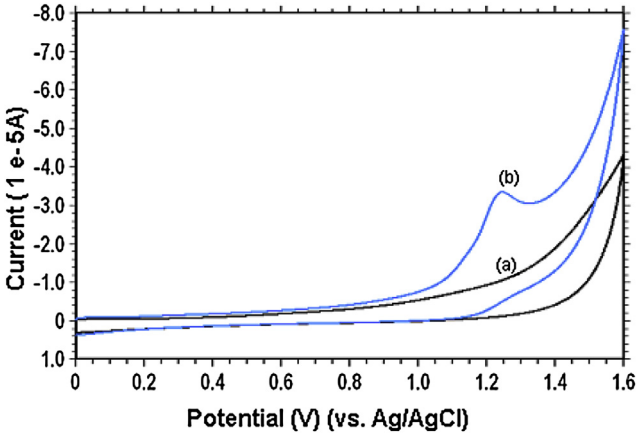


Fig. 1 – Cyclic voltammograms at the glassy carbon electrode in phosphate buffer solution (pH = 7): (a) in the presence bare pH = 7; (b) in the presence of paclitaxel (1.0×10^{-4} M) at the scan rate 0.05 Vs^{-1}.

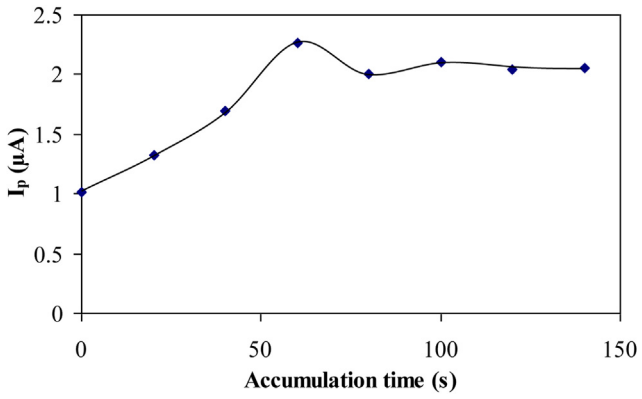


Fig. 2 – Effect of accumulation time on the oxidation peak current of 1.0 × 10^{-4} M PAC. Other conditions are same as in Fig. 1.

2.5. *Sample preparation*

Taxeleon (paclitaxel) injection is a clear, colorless to slightly yellow viscous solution. It is supplied as a nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Taxeleon is available in 100 mg in 16.67 mL. Accurately 1.42 mL of Taxeleon was pipetted and was dissolved in 100 mL methanol to obtain 1.0 mM stock solution. The mixture was allowed to stand for a few minutes with intermittent sonication to ensure complete solubility of the drug. An aliquot of this solution was transferred to a voltammetric cell and analyzed under same conditions as were used to obtain the calibration graph. Voltammograms were recorded as described for pure PAC.

To study the accuracy of the proposed method, and to check the interference from excipients used in the dosage forms, recovery experiments were carried out by the standard addition method. This study was performed by the addition of known amounts of PAC to known concentration of the dosage. The resulting mixture was analyzed as in pure PAC.

3. Results and discussion

3.1. *Cyclic voltammetric behavior of paclitaxel*

The electrochemical behavior of PAC at glassy carbon electrode was investigated using cyclic voltammetry (CV) at physiological pH = 7.0. The cyclic voltammograms obtained for 1.0 × 10^{-4} M PAC solution at a scan rate of 50 mV/s exhibit a well-defined irreversible anodic peak at about 1.245 V at glassy carbon electrode. The results are shown in Fig. 1. The voltammograms corresponding to the first cycle was generally recorded. However, no peak was observed in the reverse scan, suggesting that the oxidation process is an irreversible one. The oxidation product in turn did not show any re-oxidized or reduced peak at the extended ranges of potential which ensures that the oxidation product was not electroactive.

3.2. *Effect of accumulation parameters*

The two parameters of accumulation step, i.e., accumulation time and potential were examined. Open circuit accumulation is widely used in electro analytical chemistry to accumulate

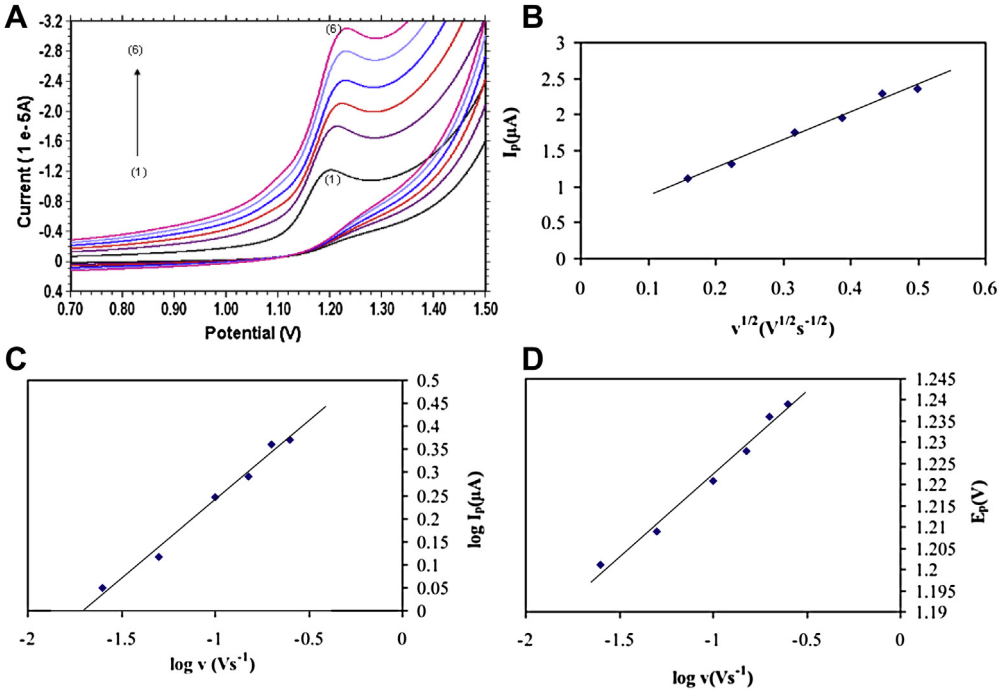


Fig. 3 – (A) Cyclic voltammograms for the oxidation of PAC at different scan rates (1) 0.025 (2) 0.05 (3) 0.1 (4) 0.15 (5) 0.2 (6) 0.25/Vs^{-1}. (B) Dependence of oxidation peak current on the square root of scan rate. (C) Linear relation between logarithm of peak current and logarithm of scan rate. (D) Dependence of oxidation peak potential on the logarithm of scan rate.

analyte and improve the determining sensitivity. The influence of accumulation time ranging from 0 to 140 s on the oxidation of PAC at GCE was as shown in Fig. 2. The current increased gradually as accumulation time increased from 0 to 60 s. However, with further increasing, the accumulation time beyond 60 s the peak current tends to be almost stable. Therefore, the optimal accumulation time of 60 s was employed in further experiments.

With the change of accumulation potential, the peak current of PAC varied slightly. So, the accumulation potential had no such effect on the peak current of PAC. Therefore the accumulation was carried out at open-circuit conditions.

3.3. *Effect of scan rate*

Useful information involving electrochemical mechanism generally can be acquired from the relationship between peak current and scan rate. Therefore, the voltammetric behavior of PAC at different scan rates was also studied using cyclic voltammetry, (Fig. 3A). Scan rate studies were carried out to assess whether the process on glassy carbon electrode was under diffusion or adsorption controlled. The influence of the square root of scan rate on the peak current showed a linear relationship in the range of 0.025–0.25 mV/s (Fig. 3B) which is of a typical diffusion controlled process [13], and the equation can be expressed as

$$I_{pa}(\mu A) = 3.8178\upsilon^{1/2}\left(V^{1/2}s^{-1/2}\right) + 0.3857,\ (r = 0.9874) \quad (2)$$

A plot of logarithm of anodic peak current vs. logarithm of scan rate gave a straight line with a slope of 0 0.44 (Fig. 3C), which is close to the theoretical value of 0.5 for a purely diffusion controlled process [14] which in turn further confirms that the process is diffusion controlled where the electroactive species of PAC diffuses from the bulk solution to a planar electrode surface. Data fit yields the equation,

$$\log I_{pa}(\mu A) = 0.4404 \log \upsilon\left(Vs^{-1}\right) + 0.5813;\ (r = 0.9880) \quad (3)$$

The E_p of the oxidation peak was also dependent on scan rate. The peak potential shifted to more positive values on increasing the scan rate, which confirms the irreversibility of the oxidation process, and a linear relationship between peak potential and logarithm of scan rate (Fig. 3D) can be expressed by the following equation:

$$E_p(V) = 0.0391 \log \upsilon\left(Vs^{-1}\right) + 1.2969,\ (r = 0.9826) \quad (4)$$

As for an irreversible electrode process, according to Laviron [15], E_p is defined by the following equation.

$$E_p = E^{0'} + \left(\frac{2.303RT}{\alpha nF}\right)\log\left(\frac{RTk^0}{\alpha nF}\right) + \left(\frac{2.303RT}{\alpha nF}\right)\log \upsilon \quad (5)$$

where α is the transfer coefficient, k^0 the standard heterogeneous rate constant of the reaction, n the number of electron transferred, υ the scan rate, and $E^{0'}$ is the formal redox potential. Other symbols have their usual meanings. Thus value of αn can be easily calculated from the slope of E_p vs. log υ. In this system, the slope is 0.0391, taking $T = 298$ K, $R = 8.314$ J/K mol, and $F = 96480$ C/mol, the αn was calculated to be 1.512. According to Bard and Faulkner [16], α can be given as

$$\alpha = \frac{47.7}{E_p - E_{p/2}}\ \text{mV} \quad (6)$$

where $E_{p/2}$ is the potential where the current is at half the peak value. So, from this we obtained the value of α to be 0.82. Further, the number of electrons (n) transferred in the electro-oxidation of PAC was calculated to be 1.84–2. The value of k^0 can be determined from the intercept of the previous plot if the value of $E^{0'}$ is known. The value of $E^{0'}$ in Eq. (5) can be obtained from the intercept of E_p vs. υ curve by extrapolating

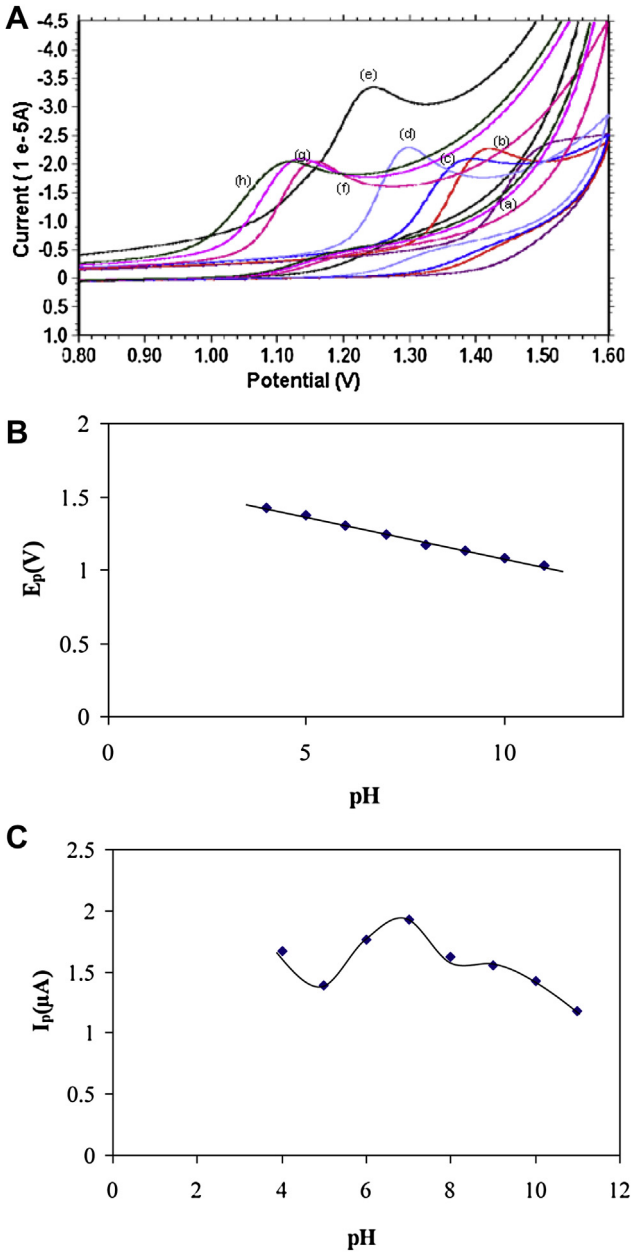


Fig. 4 – (A) Cyclic voltammograms of 1.0×10^{-4} PAC at different pH: (a) 3.0 (b) 4.2 (c) 5.0 (d) 6.0 (e) 7.0 (f) 8.0 (g) 9.2 (h) 10.4 other conditions are same as in Fig. 1. (B). Influence of pH on the potential of 1.0×10^{-4} PAC on GCE at scan rate of 50 mV/s in phosphate buffer. (C). Variation of current with pH of 1.0×10^{-4} M PAC on GCE at scan rate of 50 mV/s in phosphate buffer.

to the vertical axis at $v = 0$ [17]. In our system $E^{0'}$ was obtained as 1.2969 and the k^0 was calculated to be $2.14 \times 10^3\ s^{-1}$.

3.4. Influence of pH

The electrode reaction might be affected by pH of the medium. The electro-oxidation of 1.0×10^{-4} M PAC was studied over the pH range of 3.0–10.4 in phosphate buffer solution by cyclic voltammetry which is shown in Fig. 4A. The solution pH influenced the peak current considerably. The pH dependence of the peak potential and peak current obtained when cyclic voltammetry was used is shown in Fig. 4B and C. With the increase in pH of the solution, peak potential shifted to less positive values, (Fig. 4B), and obeys the following equation:

$$E_p(V) = 1.6439 - 0.0565\ pH; \quad (r = 0.9960) \tag{7}$$

The slope of this equation is found to be 56.5 mV/pH. This closeness of the slope to the expected theoretical value [18] of 59 mV/pH suggests that the number of electrons transferred is equal to that of the hydrogen ions taking part in the electrode reaction.

From the plot of I_{pa} vs. pH (Fig. 4C) it is clear that the intensity was increased to a high value at pH = 7.0, then the peak intensity decreased. Because the best result with respect to sensitivity accompanied with sharper response was obtained with pH = 7.0, it was selected for further experiments.

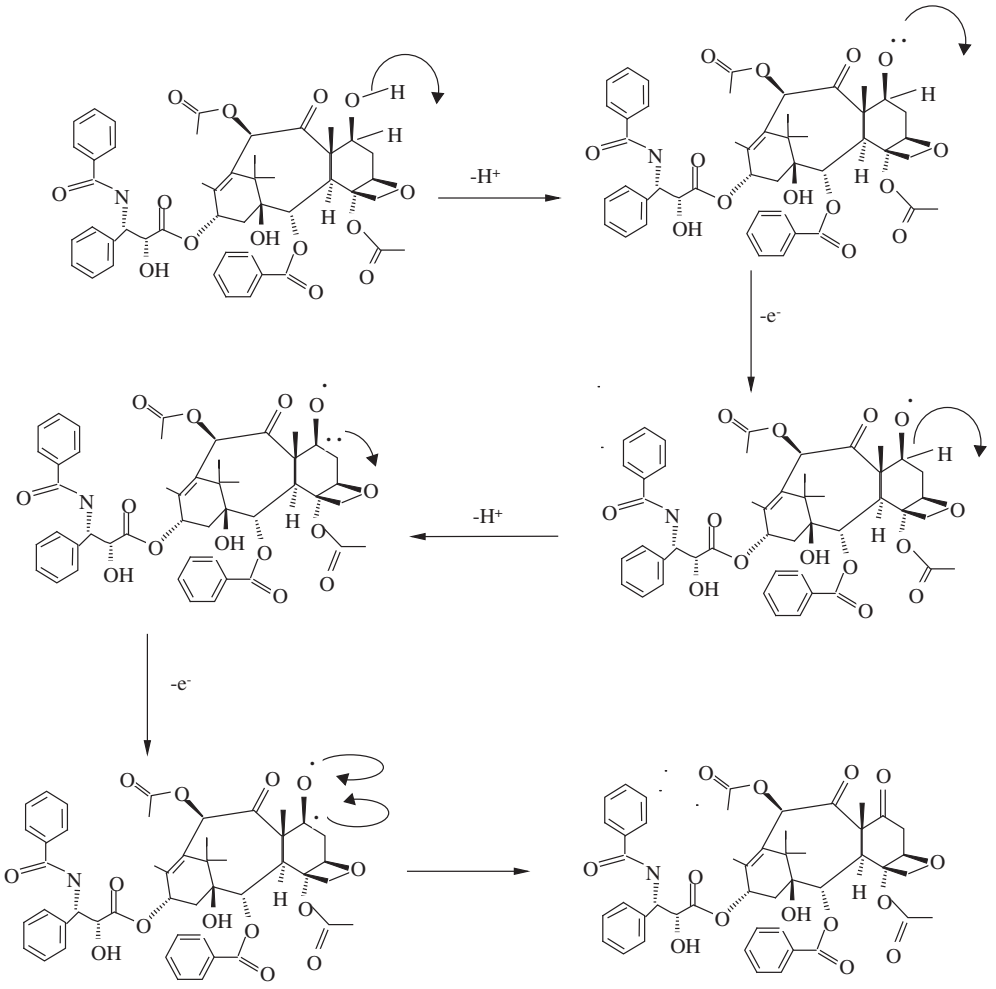
3.5. Mechanism

In the proposed method, the electro-oxidation of PAC involves two electron and two proton transfer process to form 7-oxo peclitaxel. Literature survey reveals that C-7 hydroxyl group of PAC is easily oxidized than C-2′–OH to give 7-oxo paclitaxel [19,20], (see Scheme 1). The probable mechanism is as shown in Scheme 2.

Here the hydroxyl group (-OH) is attached to the carbon atom (C-7) of the cyclohexane ring of the paclitaxel. During the electrolysis when the first proton is removed, oxygen gets a negative charge and anionic form of paclitaxel is formed. To stabilize the anionic form of the paclitaxel the hydrogen atom attached to the carbon (C-7) of the cyclohexane has undergone further electro oxidation and stable product 7-oxo paclitaxel is formed. This type of mechanism is also observed in previous reports [21].

3.6. Calibration curve

In order to develop a voltammetry method for determining the drug, we selected the differential-pulse voltammetric mode,



Scheme 2 – Probable oxidation mechanism of PAC.

because the peaks are sharper and better defined at lower concentration of PAC than those obtained by cyclic voltammetry. According to the obtained results, it was possible to apply this technique to the quantitative analysis of PAC. The phosphate buffer solution of pH = 7.0 was selected as the supporting electrolyte for the quantification of PAC as it gave maximum peak current at pH = 7.0. Differential pulse voltammograms obtained with increasing amounts of PAC showed that the peak current increased linearly with increasing concentration, shown in Fig. 5A.

The precision of the method was evaluated by repeating five experiments on the same day and in the same standard condition (repeatability) and over 2 d from the different standard solutions (reproducibility). For these studies 2×10^{-6} M paclitaxel standard solution were used. The results were given as shown in Table 1.

Using the optimum conditions described previously, linear calibration curves was obtained for PAC in the range of 1.0×10^{-6} to 1.0×10^{-5} M (Fig. 5B). The linear equation was $I_{pa} = 661{,}700\ C\ (10^{-5}\ M) + 0.8957$; ($r = 0.9943$). Deviation from linearity was observed for more concentrated solutions, due to the adsorption of PAC or its oxidation product on the electrode surface. Related statistical data of the calibration curves were obtained from five different determinations and shown in Table 1. The limit of detection (LOD) and quantification (LOQ) were 1.23×10^{-8} M and 4.10×10^{-8} M, respectively. The LOD and LOQ were calculated using the following equation:

$$\mathrm{LOD} = 3s/m;\ \mathrm{LOQ} = 10s/m \quad (8)$$

where s is the standard deviation of the peak currents of the blank (five runs), and m is the slope of the calibration curve [22]. Sample solutions recorded after 48 h did not show any appreciable change in the assay values. The detection limits reported for different classical methods are tabulated in Table 2. The present method was better as compared with other reported classical methods [4,7,10].

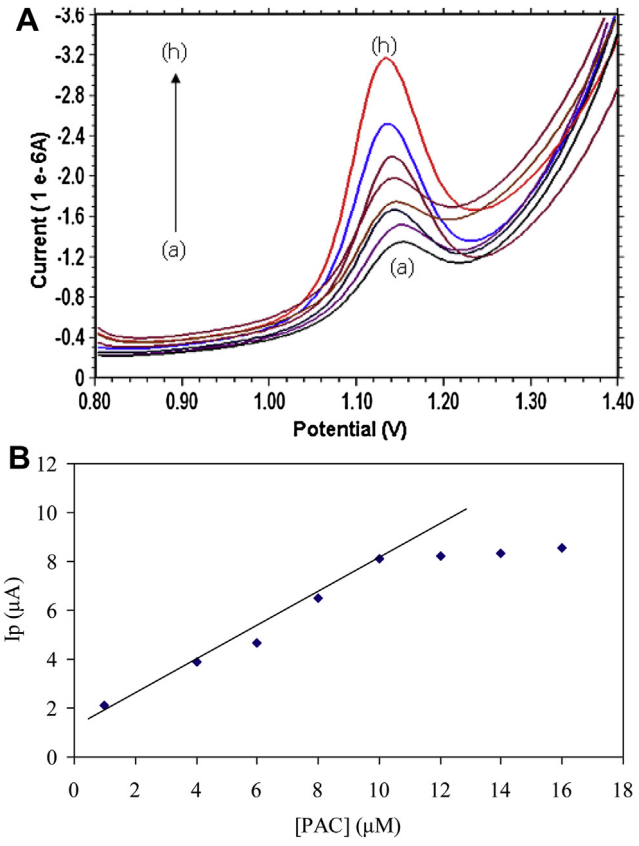


Fig. 5 – (A) Differential pulse voltammograms for increasing concentration of PAC (μM): (a) 1.0 (b) 4.0 (c) 6.0 (d) 8.0 (e) 10.0 (f) 12.0 (g) 14.0 (h) 16.0, other conditions are same as in Fig. 1. (B) Plot of current against the concentration of PAC.

Table 1 – Characteristics of PAC calibration plot using differential pulse voltammetry at glassy carbon electrode.

Linearity range	1.0×10^{-6}–1.0×10^{-5}
Slope of the calibration plot (M)	6.617×10^{-5}
Intercept	0.8957
Correlation coefficient (r)	0.9805
RSD of slope (%)	0.4094
RSD of intercept (%)	1.0675
Number of data points	8
LOD (M)	1.23×10^{-8}
LOQ (M)	4.10×10^{-8}
Repeatability of peak current (RSD %)	0.0176
Repeatability of peak potential (RSD %)	0.0013
Reproducibility of peak current (RSD %)	0.0370
Reproducibility of peak potential (RSD %)	0.0017

3.7. *Effect of excipients*

For the possible analytical application of the proposed method, the effect of some common excipients used in pharmaceutical preparations was examined. The tolerance limit was defined as the maximum concentration of the interfering substance that caused an error less than 5% for determination of PAC. The effects of these excipients on the voltammetric response was carried by analyzing sample solutions containing a fixed amount of PAC (1.0×10^{-5} M) spiked with various excess amount of each excipient under the same experimental conditions. The experimental results (Table 3) showed that hundred-fold excess of citric acid, dextrose, glucose, gum acacia, lactose, starch, tartaric acid and sucrose did not interfere with the voltammetric signal of PAC. Thus, the procedures were able to assay PAC in the presence of excipients, and hence it can be considered specific.

Table 2 – Comparison of detection limits for PAC to different classical methods.

Methods	LOD (μM)	Reference
Cysteamine/DNA/SWNTs-Film Modified au electrode (cyclic voltammetry)	8.86	[4]
RP-HPLC method	0.0351	[7]
HPLC method	1.96	[10]
Glassy carbon electrode	0.0123	Present work

Table 3 – Influence of potential excipients on the voltammetric response of 1.0×10^{-5} M PAC.

Excipients (1.0 mM) + drug (1.0×10^{-5})	Potential observed (V)	Signal change (%)
Only Paclitaxel	1.161	0
Citric acid + PAC	1.170	+0.77
Dextrose + PAC	1.163	+0.17
Glucose + PAC	1.160	−0.08
Gum acacia + PAC	1.163	+0.17
Lactose + PAC	1.160	−0.08
Sucrose + PAC	1.158	−0.25
Tartaric acid + PAC	1.171	+0.86
Starch + PAC	1.158	−0.25

Table 4 – Recovery test of PAC in Taxeleon injection.

Added (M)	Found (M)[a]	Recovery (%)	Bias (%)	S.D. ± R.S.D. (%)
3.0×10^{-6}	2.980×10^{-6}	99.33	0.67	0.023 ± 0.789
5.0×10^{-6}	5.020×10^{-6}	100.4	0.40	0.079 ± 1.562
8.0×10^{-6}	7.890×10^{-6}	98.62	−1.37	0.071 ± 0.911
1.0×10^{-5}	0.998×10^{-5}	99.8	−0.20	0.019 ± 1.940
3.0×10^{-5}	3.102×10^{-5}	103.4	3.40	0.0481 ± 1.523
5.0×10^{-5}	4.989×10^{-5}	99.78	−0.22	0.072 ± 1.440
8.0×10^{-5}	8.021×10^{-5}	100.26	0.26	0.120 ± 1.488

[a] Average of five determinations.

3.8. *Injection analysis and recovery test*

In order to evaluate the applicability of the proposed method in the pharmaceutical sample analysis, it was used to detect PAC in "Taxeleon" injection (100 mg in 16.67 mL). The procedure for the injection analysis was followed as described in the procedural section. The results are in good agreement with the content marked in the label. The detected content was 100 mg per injection with 103.4% recovery.

The recovery test of PAC ranging from 3.0×10^{-6} to 8.0×10^{-5} M was performed using differential-pulse voltammetry. Recovery studies were carried out after the addition of known amounts of the drug to various pre-analyzed formulations of PAC. The results are listed in Table 4. The recoveries in different samples were found to lie in the range from 98.6% to 103.4% with R.S.D of 0.911%–1.523%.

3.9. *Detection of paclitaxel in urine samples*

The developed differential voltammetric method for the PAC determination was applied to urine samples. The recoveries from urine were measured by spiking drug free urine with known amounts of PAC. A quantitative analysis can be carried out by adding the standard solution of PAC into the detect system of urine samples, and the peak linearly increased in height. The calibration graph was used for the determination of spiked PAC in urine samples. The detection results of four urine samples obtained are listed in Table 5. The recovery determined was in the range from 97.7% to 101.0% and the RSD and SD values given in Table 5.

Table 6 – Response of peak current of 7 μM paclitaxel in urine sample at different time intervals.

Time (min)	Peak current (μA)	Concentration (μM)
20	6.458	6.64
40	5.954	6.12
60	5.245	5.39
80	4.467	4.59
100	4.115	4.23
120	3.894	4.00
140	3.114	3.20
160	2.985	3.06
Elimination rate constant	0.245 h^{-1}	
Half life of drug	2.827 h	

3.10. *Pharmacokinetics study*

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion. Clinical pharmacokinetics is the application of pharmacokinetic principles to the safe and effective therapeutic management of drugs in an individual patient. Primary goals of clinical pharmacokinetics include enhancing efficacy and decreasing toxicity of a patient's drug therapy. The development of strong correlations between drug concentrations and their pharmacologic responses has enabled clinicians to apply pharmacokinetic principles to actual patient situations. A drug's effect is often related to its concentration at the site of action, so it would be useful to monitor this concentration. Receptor sites of drugs are generally inaccessible to our observations or are widely distributed in the body, and therefore direct measurement of drug concentrations at these sites is not practicable. We cannot directly sample drug concentration in this tissue. However, drug concentration in the blood or plasma, urine, saliva, and other easily sampled fluids can be measured.

Response of peak current at different time interval for 7 μM concentration of paclitaxel in urine sample is as shown in

Table 5 – Determination of PAC in urine samples.

Sample	Spiked (10^{-5} M)	Found[a] (10^{-5} M)	Recovery (%)	Bias (%)	S.D. ± R.S.D (%)
1	1.0×10^{-6}	1.01×10^{-6}	101.0	1.00	0.019 ± 0.014
2	4.0×10^{-6}	4.00×10^{-6}	100.0	0.20	0.017 ± 0.012
3	6.0×10^{-6}	6.02×10^{-6}	100.3	0.34	0.0155 ± 0.011
4	8.0×10^{-6}	7.92×10^{-6}	99.0	−1.00	0.036 ± 0.026
5	10.0×10^{-6}	9.77×10^{-6}	97.7	−2.30	0.155 ± 0.109

[a] Average of five determination.

Table 6. From the plot of urine drug concentration vs. time (supplementary Fig. S1) the pharmacokinetics data can be calculated. Some of the pharmacokinetics data calculated are listed in Table 6.

4. Conclusion

The voltammetric oxidation of PAC at glassy carbon electrode in phosphate buffer solution under physiological condition, i.e., pH = 7.0, has been investigated. Paclitaxel undergoes two electron − two proton change and is a diffusion-controlled process. A suitable oxidation mechanism was proposed. The peak current was linear to PAC concentrations over a certain range, under the selected conditions. This helps in voltammetric determination of selected analyte as low as 1.23×10^{-8} M and can be used successfully to assay the drug in pharmaceutical dosage form as well as in spiked urine samples. High percentage recovery and study of excipients showed that the method is free from the interferences of the commonly used excipients and additives in the formulations of drugs. In addition, the results obtained in the analysis of PAC in spiked urine samples demonstrated the applicability of the method in real sample clinical analysis. The proposed method is suitable for quality control laboratories as well as pharmacokinetic studies where economy and time are essential.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ajps.2013.11.007

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