

# **Edelweiss Chemical Science Journal**

#### Research Article

ISSN 2641-7383

## Spot on Gold Nanoparticles/Silica Modified Electrode for Rapid Sensitive Determination of Dinoprostone

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Citation: Atty SA, Walash M, Toubar S, AbouEl-Alamin MM, Elabd EA, et al. Spot on gold nanoparticles/silica modified electrode for rapid sensitive determination of dinoprostone (2019) Edelweiss Chem Sci J 2: 17-22

**Received:** May 05, 2019 **Accepted:** June 06, 2019 **Published:** June 25, 2019

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#### Abstract

A novel simple and selective electrochemical procedure is utilized for the determination of Dinoprostone (DIN) in drug substance and pharmaceutical preparation with good recovery and without interference with other excipient. Herein, the electrochemical sensing platform based upon preparing gold nanoparticle sensor on silica modified carbon paste electrode. The surface morphology of the modified electrode was characterized by scanning electron microscope. Different experimental conditions, including electrode composition, effect of pH and scan rate were estimated carefully by cyclic voltammetry to obtain the highest electrochemical response. By using square wave voltammetry a good linear response was obtained in the range of,  $2 \times 10^{-5}$ -4  $\times 10^{-4}$  mol L<sup>-1</sup>, and  $2 \times 10^{-7}$ -1.6  $\times 10^{-4}$  mol L<sup>-1</sup>, with low detection limit of  $5 \times 10^{-6}$  mol L<sup>-1</sup>, and 4.9  $\times 10^{-8}$  mol L<sup>-1</sup> by CPE and GNP/SMCPE respectively. The obtained results are in good agreement with those obtained by official method. No electrochemical method was reported before for determination of DIN. The developed method was simple, rapid, economic and challenging to green analytical chemistry.

Keywords: Dinoprostone, Square wave voltammetry, Sensor, Carbon paste electrode, Gold nanoparticles/silica.

Abbreviation: DIN-Dinoprostone; CPE-Carbon Past Electrode; SMCPE-Silica Modified Carbon Past Electrode; GNP/SMCPE-Gold Nano-Partical / Silica Modified Carbon Past Electrode; CV-Cyclic Voltammetry; SWV-Square Wave Voltammetry.

#### Introduction

Prostaglandins are essential mediator that are formed in many tissues and adjust many physiological functions, over normal and/ or patho physiological conditions [1-3]. They have many functions, as, the role of bone cells in establishing the hematopoietic stem cell, immunotherapy of cancer, female reproduction, platelet receptors, type I collagen structure, synthesis, and regulation nonsteroidal anti-inflammatory drugs for osteoarthritis [4] (**Figure 1**).

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Figure 1: Dinoprostone (DIN) chemical structure.

Dinoprostone (DIN) in medicine identified as Prostaglandin E2, (Z)-7-[(1R,2R,3R,5S)-3,5-dihydroxy-2-[(E,3S)-3-hydroxyoct-1-enylcyclopentyl] hept-5-enoic acid is a naturally occurring prostaglandin used in medicine to induce labor and as an abortifacient

[5,6]. Dinoprostone stimulates myometrial contractions in the gravid uterus that are similar to the contractions that occur in the term uterus during labor [7,8]. These contractions are usually sufficient to cause abortion [9].

Few analytical methods were developed and validated for determination of dinoprostone in drug substance, dosage form, human gastric mucosa, and in cultured tumor cells using HPLC with UV, laser induced fluorescence and electrospray ionization tandem mass spectrometric detectors. GC-MS was used also for determination of the drug in cultured tumor cells [10].

Due to the important biological role of prostaglandins, fast, simple and sensitive electrochemical method has to be developed for determination of DIN. Carbon Paste Electrodes (CPE) has been widely applied in the field of electrochemistry for the determination of low analyte concentrations due to their ease of fabrication, low cost and high sensitivity [11].



Modification of electrodes with various modifiers has been reported in recent years to improve sensitivity, selectivity, and detection limit [12-14]. Silica gel can be incorporated in paste with carbon and used as modifier. It has high adsorption capacity, insolubility in most solvents, and thermal stability, and high surface area of synthetic silica makes it valuable as support for various catalysts [15-20]. Gold Nanoparticles (GNPs) with large surface area, good biocompatibility, and high conductivity and electro catalytic activity have been used to increase sensitivity and improve detection limits [21-27].

The literature survey revealed that no attempt had been made to study the voltammetric behavior of dinoprostone. Therefore, the aim of the present work was to prepare a new sensor based on gold nanoparticles, silica, and graphite for rapid and selective electroanalytical determination of DIN in drug substance and pharmaceutical product. Moreover the prepared electrode was characterized and the surface area was calculated.

#### **Experimental**

#### Materials and reagents

Dinoprostone was kindly supplied from Amriya Pharmaceutical Co., Egypt, and its purity was found to be 98.53% according to USP Pharmacopiea. Dinoglandin E2 (batch NO. 09477, Alexandria Co. for Pharmaceutical and Chemical Industeries) was labeled to contain 3 mg DIN per vaginal tablet. It was purchased from the local market. Silica gel was purchased from Sd. fine Chem. Ltd. Mumbai. Hydrogen tetrachloroaurate (HAuCl<sub>4</sub>) across organics New Jersey batch NO. AO321694 was purchased from Sigma-Aldrich. Britton-Robinson buffer (B-R buffer) was prepared by mixing different volumes of 0.04 M in H<sub>3</sub>PO<sub>4</sub> (Adwic Co., Egypt), 0.04 M acetic acid (LOBA-Chemic Co., India), and 0.04 M boric acid (Polski EODZNN Chemiczne S.A. Co., Poland) with the appropriate amount of 0.2 M NaOH (Adwia Co., Egypt) to obtain the desired pH of 2.0-9.0. Buffer solutions were kept in a refrigerator [28]. All solutions were prepared from chemicals of analytical grade, and sterilized Milli-Q deionized water was used.

#### **Standard solutions**

Stock standard solution of dinoprostone  $(1 \times 10^{-2} \text{ M})$  was prepared by dissolving appropriate amount of the drug in deionized water.

#### **Preparation of electrodes**

Carbon Paste Electrode (CPE) was prepared by mixing graphite powder (0.5 g) with paraffin oil (0.3 mL) in a glassy mortar. The carbon paste was packed into the hole of the electrode body and smoothed on a filter paper until its shiny appearance. Modified silica gel CPE (SMCPE) was prepared by mixing graphite powder with 5 % of its weight with silica gel. For better homogeneity, the resulting composite was dispersed in ethanol and stirred on a magnetic stirrer until the solvent completely evaporated, then about 3 mL of paraffin oil was added.

Gold silica modified electrode was prepared by immersing silica gelmodified CPE (SMCPE) composite into 6 mM hydrogen tetrachloroaurate (HAuCl $_4$ ) solution containing 0.1 M KNO $_3$  [29]. All the prepared electrodes were washed with double distilled water and dried carefully with a paper without touching the surface and then left to dry in air for 10 min before being used.

#### Instrumental and experimental setup

All voltammetric measurements were performed using A Bio-logic SP 150 electrochemical workstation. A One compartment cell and the three electrodes were connected to the electrochemical workstation through a C3-stand. A platinum wire from BAS (USA) was employed as the auxiliary electrode. The electrode potentials were measured with

respect to the reference electrode Ag/AgCl electrode from BAS (USA). Sigma Plot 11 was used for the transformation of the initial signal. A Cyberscan 500 digital (EUTECH Instruments, USA) pH meter with a glass combination electrode served to carry out the pH measurement. Scanning Electron Microscopy (SEM) measurements were carried out using a JSM-6700F scanning electron microscope (Japan Electro Company). All the electrochemical experiments were performed at an ambient temperature of 25°C.

#### **Electroanalytical measurements**

Construction of calibration curve of dinoprostone; Aliquots equivalent to (0.1-2.0 mL), and (1-800  $\mu L)$  from  $1\times 10^{-3}$  M solutions of DIN were transferred into a series of 5-mL volumetric flasks for CPE and GNP/SMCPE respectively, using micropipette, and the volume was completed to the mark with B-R buffer pH 2. This solution was transferred to the electrolytic cell, and then Square Wave Voltammogram (SWV) was recorded. The peak current was measured at a scan rate of 10 mV s $^{-1}$  using gold nanoparticles silica gel-modified CPE (GNP/SMCPE). Calibration curve was constructed by plotting the peak currents against drug concentrations.

#### Application to pharmaceutical product

Commercial pharmaceutical samples containing DIN was analyzed to evaluate the validity of the proposed method. Five vaginal tablets were finely mixed, and a weight equivalent to 15 mg of dinoprostone was dissolved in 30 mL of deionized water. Then 1.4 mL was transferred quantitatively to a 100 mL volumetric flask and completed to the mark with deionized water to obtain 10<sup>-3</sup> M. Appropriate dilutions with deionized water were done to prepare samples in the quantification range.

#### **Results and Discussion**

#### Morphologies of different electrodes

The response of an electrochemical sensor was related to its physical morphology. The morphology of bare CPE (A), SMCPE (B), and GNP/SMCPE (C) were shown in **Figure 2**.

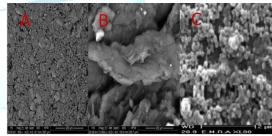


Figure 2: Scanning electron microscope images of (A) bare CPE, (B) SMCPE and (C) GNP/SMCPE.

The SEM image of CPE shows that its surface was characterized by a compact surface, isolated and irregularly shaped graphite, while the SEM image of GSMCPE shows that metallic nanoparticles are located at different elevations over the substrate. Moreover, a porous nanostructured film of gold nanoparticles was noticed which extremely enhanced the active surface area of GNP/SMCPE and might be very important to promote electron transfer.

#### **Electrochemistry of dinoprostone**

Preliminary investigation using cyclic voltammetry shows a behavior of irreversible oxidation of DIN at bare CPE, SMCPE, and GNP/SMCPE. **Figure 3** shows typical cyclic voltammograms of  $1.0 \times 10^{-2}$  mol L<sup>-1</sup> of DIN, in B-R buffer pH 2.0, at a scan rate of 100 mV s<sup>-1</sup>,



recorded at three electrodes under investigation. At bare CPE, the oxidation peak current was observed to be 30.4  $\mu$ A, while in the case of SMCPE, the oxidation peak current was found to be 40.1  $\mu$ A and the best one is GNP/SMCPE, which has a value of 80  $\mu$ A.

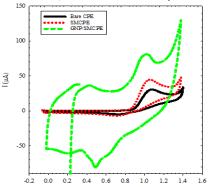
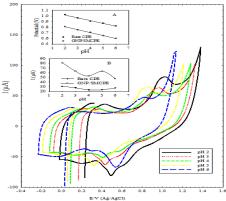


Figure 3: Cyclic voltammograms of  $1.0 \times 10^{-2}$  mol L<sup>-1</sup> of DIN in B-R buffer pH 2, at a scan rate of 100 mV s<sup>-1</sup> recorded at different working electrodes (i.e., bare CPE, SMCPE and GNP/SMCPE).

The potential of different electrodes were found in order of, bare CPE, SMCPE, and GNP/SMCPE respectively (1.13 V compared to 1.12 V, and 1.16 V), due to the improvement in the reversibility of the electron transfer process and a larger real surface area of the modified electrode. The electro deposition of gold nanoparticles on GNP /SMCPE resulted in an observable increase in the peak current, which indicated an improvement in the electrode kinetics and increase in the potential of oxidation substantial, where GNP/SMCPE acts as a cation exchange [29,30] that attracts the positively charged DIN.

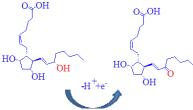
#### **Selection of the Optimum Experimental Conditions**

Effect of pH: In order to ascertain that electrocatalytic oxidation of DIN would be pH dependent, the voltammetric response of DIN was investigated in solutions with varying pH from 2.0 to 6.0 in order to optimize the electrocatalytic response. Figure 4 shows the cyclic voltammograms of the oxidation peak currents of DIN at different pH values using B-R buffer at bare CPE, and GNP/SMCPE electrode. Higher anodic current for DIN at pH 2 is due to major microspecies at this pH.



**Figure 4:** Cyclic voltammetric response of  $1.0 \times 10^{-3}$  mol L<sup>-1</sup> DIN at GNP/SMCPE using 0.04 M B-R buffers of different pH values, inset (A) shows the relation between anodic peak potential of DIN versus pH using bare CPE and GNP/SMCPE, Inset (B) shows the relation between anodic peak current of DIN versus pH using bare CPE and GNP/SMCPE.

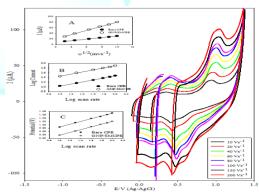
Moreover, DIN oxidation is a one-electron process, which may be attributed to the oxidation of double bonds [31-33]. DIN carries positive charge that can be attracted by the negative charge of the electrode; the suggested electrochemical oxidation of DIN was depicted in **Scheme 1**.



Scheme 1: Suggested oxidation mechanism of dinoprostone.

A comparison between the anodic peak current at different pH values of bare CPE, and GNP/SMCPE show that GNP/SMCPE displays higher anodic current for DIN than bare CPE which indicates the effect of gold on the catalytic oxidation processes as shown in Figure 2. It is observed that as the pH values increase, the peak potential shifts toward less positive values, which indicates the participation of protons in the electrode process and that the electrocatalytic oxidation of DIN is a pH-dependent reaction. The relationship between the anodic peak potential and the solution pH value at bare CPE and GNP/SMCPE could be fit to the linear regression equation of E<sub>pa</sub> (V)=1.1132-0.0493 pH, with a correlation coefficient of r=0.9973 and E<sub>pa</sub> (V)=0.9118-0.0521 pH, with a correlation coefficient of r = 0.9994 respectively. The slope was found to be 49.3 mV/pH and 52.1 mV/pH units at bare CPE and GNP/SMCPE respectively over the pH range from 2 to 6, which is close to the theoretical value of -48.3 mV. This indicated that the number of protons and transferred electrons involved in the oxidation mechanism are equal [34].

**Effect of scan rate:** The interfacial reaction of the drug at each electrode was identified by recording the cyclic voltammograms of  $1 \times 10^{-3}$  M solution at different scan rates (v) 10-250 mV s<sup>-1</sup> in B-R buffer (pH 2.0). Typical CV curves of DIN at different scan rates were shown in **Figure 5**.



**Figure 5:** Cyclic voltammograms of  $1.0 \times 10^{-3}$  mol L<sup>-1</sup> DIN at GNP/SMCPE in 0.04 M B-R buffer pH 2 from 10 to 200 mV s<sup>-1</sup>, Inset A: plot of  $I_p$  vs.  $v^{1/2}$ . Inset B: plot of log  $I_p$  vs. log v. Inset C: plot of Ep vs. log v.

Figure 5 inset A showed that the peak current increased linearly with increasing the square root of scan rate up to a scan rate of 100 mV s<sup>-1</sup>, according to regression equation [35]:

$$i_p = (2.69 \text{ x } 105) \text{ n}^{-3/2} \text{ A C}_0 \text{ x D}_0^{-1/2} v^{1/2}$$



In this equation, ip is the peak current density (µA cm<sup>-2</sup>), n is the number of electrons appearing in half-reaction for the redox couple, v is the scan rate at which the potential is swept (V s<sup>-1</sup>), C is the analyte concentration, A is the electrode area (0.071 and 0.118 cm<sup>2</sup> for bare CPE, and GNP/SMCPE respectively), and  $D_{\scriptscriptstyle 0}$  is the electroactive species diffusion coefficient (cm2 s-1). The apparent diffusion coefficient, Dapp, of DIN in B-R buffer (pH 2) was calculated from Cyclic Voltammetry (CV) experiments which increases from  $8.9 \times 10^{-7}$ cm<sup>2</sup> s<sup>-1</sup> in case of using bare CPE to  $4.3 \times 10^{-5}$  cm<sup>2</sup> s<sup>-1</sup> after the functionalization of bare CPE surface with gold nanoparticles. This indicated the quick mass transfer of the analyte molecules toward GNP/SMCPE surface from bulk solutions and fast electron transfer process of electrochemical oxidation of the analyte molecule at the electrode-solution interface. The calculated D<sub>app</sub> values also showed that gold improves the electron transfer kinetics at the electrode/solution interface, suggesting that the reaction is a diffusioncontrolled electrode reaction.

Direct proportionality was obtained between log current and log scan rate in range of  $10\text{-}100~\text{mV}~\text{s}^{\text{-}1}$  (Figure 5 inset B), giving the following equation:

 $\begin{array}{ll} log \ I \!\!=\!\! 0.6003 \!\!+\!\! 0.435 \ log \ v \\ log \ I \!\!=\!\! 1.0134 \!\!+\!\! 0.444 \ log \ v \\ \end{array} \qquad \begin{array}{ll} r \!\!=\!\! 0.9994 \ for \ Bare \ CPE \\ r \!\!=\!\! 0.9992 \ for \ GNP/SMCPE \end{array}$ 

The value of the slope of the obtained linear relations is less 0.5 which implies that the electroactive species are transported by a diffusion process with an adsorption contribution [36]. From the different investigated scan rates, the 100 mVs<sup>-1</sup> gave the best voltammograms and higher selectivity.

The electrochemical oxidation peak potential  $(E_p)$  was also dependent on the scan rate, where increasing the scan rate resulted in a shift to more positive potentials, as shown in Figure 5 inset C.

 $\begin{array}{ll} E_p(V) = 0.9046 + 0.0823 \ log \ v(Vs^{\text{-}1}) & r = 0.9993 \\ E_p(V) = 0.8562 + 0.0819 \ log \ v(Vs^{\text{-}1}) & r = 0.9996 \end{array}$ 

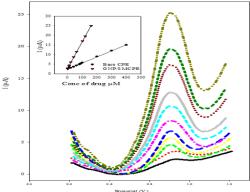
In order to determine the kinetic parameters of the electron-transfer process for the DID oxidation on the GNP/SMCPE, Laviron's theory [37,38] for irreversible processes was applied to calculate the number of electron transferred.

 $E=E^{\circ}+2.303 \text{ RT/}\alpha nF[\log RTK^{\circ}/\alpha nF]+2.303RT/\alpha nF(\log v)$ 

Where, R is the gas constant (8.314 J K mol<sup>-1</sup>), T is the temperature (298 K), F is the faraday constant (96485 Cmol<sup>-1</sup>),  $\alpha$  is the electron transfer coefficient, and n is the number of the electrons and  $\alpha$ n can be calculated from the slope of potential against log scan rate. In this system, the slope were 0.0823 and 0.0819,  $\alpha$ n was calculated to be 0.719 and 0.720 for bare CPE and modified electrode respectively, since for a totally irreversible electron transfer,  $\alpha$  assumed as 0.5, then n was calculated to be 1.4 which indicated that one electron were involved in the oxidation of DIN.

#### Method validation

**Linearity, LOD, and LOQ:** Under the above optimum conditions, the linearity using SWV was carried out where good correlation between the oxidation peaks current (I) and concentration was found in ranges of  $2x10^{-5}$ –4  $x10^{-4}$  mol L<sup>-1</sup>, and  $2x10^{-7}$ –1.6 $x10^{-4}$  mol L<sup>-1</sup> using bare CPE, and GNP/SMCPE (**Figure 6**). The Limits of Detection (LOD) and the Limits of Quantitation (LOQ) were calculated from the oxidation peak currents of the linear ranges according to ICH guideline [39]. LOD and LOQ values confirmed the sensitivity of GNP/SMCPE over bare CPE. The calibration equation parameters and necessary validation data are shown in **Table 1**.



**Figure 6:** Square wave voltammograms for different concentrations of dinoprostone at GNP/SMCPE using B-R buffer pH 2. Inset: the calibration curve of the peak current values against the concentration of DIN at bare CPE in range (2 x 10<sup>-5</sup>-4 x 10<sup>-4</sup> mol L<sup>-1</sup>) and GNP/SMCPE in range (2 x 10<sup>-7</sup>-1.6 x 10<sup>-4</sup> mol L<sup>-1</sup>).

Parameters	CPE	GNP/SMCPE			
Linearity (M)	2 x 10 <sup>-5</sup> -4 x10 <sup>-4</sup>	2 x 10 <sup>-7</sup> -1.6 x 10 <sup>-4</sup>			
LOD (M)	5 x 10 <sup>-6</sup>	4.9 x 10 <sup>-8</sup>			
LOQ (M)	15 x 10 <sup>-6</sup>	1.47 x 10 <sup>-7</sup>			
Slope	0.1394	0.0317			
SE of slope	0.0015	0.0004			
Intercept	2.8931	2.4593			
SE of Intercept	0.1044	0.0668			
Correlation coefficient	0.9995	0.9996			
(r)					
Accuracy	$100.53 \pm 1.152$	$99.58 \pm 0.853$			
Mean <sup>a</sup> ± SD%					
Precision <sup>b</sup> (RSD%)	0.599	0.745			
Repeatability	0.697	0.786			
Intermediate precision					

a average of five experiments, bn=9.

**Table 1:** Results of validation protocol for quantitative determination of dinoprostone by the proposed square wave voltammetry.

Accuracy: The accuracy of the proposed method for determination of DIN in drug substance was shown in Table 1. The mean percentage recoveries were evaluated and satisfactory results were obtained. The accuracy was further assessed by application of standard addition technique (Table 2).

**Precision:** The intraday and interday precision were assessed by analyzing three concentration levels in triplicate in a single assay run, and on three separate assay runs for the drug, RSD% were less than 2%. This level of precision was adequate for the quality control analysis of the drug as shown in Table 1.

**Robustness:** The robustness of the proposed method was demonstrated by constancy of the peak current with deliberated minor changes in the experimental parameters. The studied variables included; the change in pH  $(2.0 \pm 0.2)$ . These minor changes that may take place during the experimental operation did not affect the peak current intensity of the studied drug, indicating the reliability of the proposed method during normal usage.



### Application of the proposed SWV method for the determination of dinoprostone in pharmaceutical preparation

The proposed SWV method was successfully applied to determine DIN in its pharmaceutical formulation. The obtained results are listed in **Table 2**. The specificity of the proposed SWV voltammetric method was proven by its ability to determine DIN in pharmaceutical formulation without interference from excipients that commonly present.

Pharmaceutical	Proposed SWV	Conc. taken	Conc. found	Recoverya%		
formulation	methods	M	M	·		
Dinopost vagina tab. (3	Bare CPE	8 x 10 <sup>-5</sup>	7.9 x 10 <sup>-5</sup>	98.75 ± 1.726		
mg of Dinoprostone / tab)	GNP/SMCPE	4 x 10 <sup>-5</sup>	3.942 x 10 <sup>-5</sup>	98.55 ± 0.837		
Standard addition technique						
Proposed SWV methods	Conc. of claimed	Pure added M	Pure found M	Recoverybo of		
	taken			pure added		
		4 x 10 <sup>-5</sup>	3.961 x 10 <sup>-5</sup>	99.03		
Bare CPE	8 x 10 <sup>-5</sup> M	10 x 10 <sup>-5</sup>	9.9 x 10 <sup>-5</sup>	99.00		
		20 x 10 <sup>-5</sup>	19.86 x 10 <sup>-5</sup>	99.30		
Mean $\pm$ SD 99.11 $\pm$ 0.165						
		2 x 10 <sup>-5</sup>	1.989 x 10 <sup>-5</sup>	99.45		
GNP/SMCPE	4 x 10 <sup>-5</sup> M	8 x 10 <sup>-5</sup>	7.966 x 10 <sup>-5</sup>	99.58		
		12 x 10 <sup>-5</sup>	12.1 x 10 <sup>-5</sup>	100.83		
Mean ± SD				99.95±0.762		

<sup>a</sup>Recovery of five different determinations.
<sup>b</sup>Mean of three determinations.

**Table 2:** Determination of dinoprostone in drug product and application of standard addition technique by the proposed SWV methods.

In addition, the validity of the proposed SWV method was assessed by the standard addition technique, Table 2.

Statistical comparison between the results obtained by the proposed method and the official method using student t-test and F ratio revealed no significant differences with respect to accuracy and precision at probability 0.05% and the data was presented in **Table 3**.

Values	Propose	d SWV methods	Official method
	CPE	GNP/SMCPE	
Mean <sup>a</sup>	100.53	99.58	100.07
SD	1.152	0.853	1.07
n	5	5	5
Variance	1.327	0.728	1.145
t (2.306) <sup>b</sup>	0.654	0.801	
F (6.388) <sup>b</sup>	1.159	1.573	

<sup>a</sup>Average of five determinations.

#### Conclusion

Inexpensive and eco-friendly SWV method was developed and validated for rapid sensitive determination of DIN in drug substance and pharmaceutical dosage form. The literature review revealed no attempted had been made for electrochemical determination of DIN. The proposed method was based on the electrochemical oxidation of DIN at both bare CPE and gold nanoparticle/silica-modified CPE as a new fabricated sensor which causes an enhancement in the anodic peak current. The results indicate the validity of the methods for application in routine quality control, since it is characterized by high reproducibility and selectivity.

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The values between parenthesis are the corresponding theoretical values of t and F at P = 0.05. **Table 3:** Statistical comparison between the proposed and official methods for the determination of dinoprostone in drug substance.

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