

## Plastic Membrane Electrodes of Coated Wire Type for Micro Determination of Quininium Cation in Pharmaceutical Tablets

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**Abstract: Problem statement:** Silver and copper all-solid state wire sensor electrodes of quininium cation with different ion exchangers have been prepared and used in pharmaceutical analysis. A comparative study with a reference method is applied in order to investigate the validity of the proposed method for potentiometric analysis of pharmaceutical compounds containing quinine. **Approach:** A Nernstian equation was proved for all electrodes of quinine in this research. Potentiometric investigations were carried out to identify the characteristic performance of the electrodes, such as the life span, pH effect and effect of the interfering ions. Chemometric and statistical studies of the chemical analysis of quinine in pharmaceutical compounds were applied using different type of electrodes compared to a reference method. **Results:** A Polyvinyl Chloride (PVC) membrane electrodes of silver (Ag) and Copper (Cu) Coated Wire Electrodes (CWEs) were prepared for quininium cation ( $\text{Qn}^+$ ). The ion exchangers were ion-pairs and ion associates of  $\text{Qn}^+$  with different counter-anions, such as reineckate ( $\text{Rn}^-$ ), phosphotungstate ( $\text{PT}^{3-}$ ) and phosphomolybdate ( $\text{PM}^{3-}$ ). The Qn-CWEs showed a Nernstian response for a maximum 24 h at 25°C, except with that based on Cu-Qn<sub>3</sub>PM. **Conclusion/Recommendations:** The ion pair QnRn and the ion associates Qn<sub>3</sub>PT and Qn<sub>3</sub>PM are very efficient ion exchangers for the construction of Qn-CWEs. The performance characteristics (life span, pH effect and the selectivity) proved that such electrodes can be successfully used for the potentiometric micro-determination of  $\text{Qn}_2\text{SO}_4$  in its pharmaceutical preparation. The analytical application showed that the recoveries and relative standard deviation of different Qn-CWEs reveals a high degree of accuracy and precision. In spite of their high accuracy, the F- test conclude the fact that the reference method is usually more precise than proposed method introduced in this study except for Ag-Qn<sub>3</sub>PM electrode. In general, Ag-Qn<sub>3</sub>PM CWE showed a discrete behavior regarding accuracy and silver metal preference. Further application of this type of electrodes on different pharmaceutical compounds is recommended to countervail the trends on the performance characteristics and confront the statistical parameters.

**Key words:** Most ion-Selective Electrodes (ISEs), Phosphotungstic Acid (PTA), polyvinyl chloride, pharmaceuticals samples, Separate Solution Method (SSM), Matched Potential (MPM), pharmaceutical compounds, reference method, plastic membrane

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### INTRODUCTION

Ion-selective electrode is an electrochemical sensor based on thin films or selective membranes as recognition elements in aqueous solutions. Coated Wire Electrodes (CWEs), introduced by Freiser in the mid-1970s, are prepared by (Pt, Ag, Cu) or graphite-based with any conventional shape, such as wire or disk. The conductor is usually dipped in a solution of PVC and the active substance and the resulting film is allowed to

air-dry. They are usually highly sensitive and very easy to use. An ion-selective membrane is the key component of all potentiometric ion sensors. The membrane establishes the preference with which the sensor responds to the analyte in the presence of various interfering ions (Lonsdale, 1982; Wang, 2006; Mirbaghei *et al.*, 2007; Emamieh *et al.*, 2008). Such a membrane is quite similar to liquid phase, because diffusion coefficients for dissolved low molecular weight ion-pairs or ion-associates are in the order of

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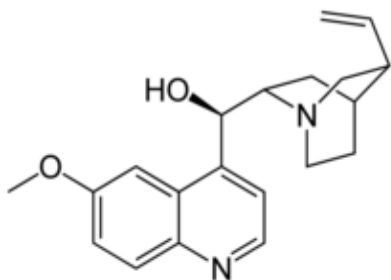


Fig. 1: Structural formula of quinine

$10^{-7}$ - $10^{-8}$   $\text{cm}^2 \text{sec}^{-1}$  (Mikehelson, 1994; Schaller *et al.*, 1994; Jamhour, 2005; Saito *et al.*, 2008). The ion-selective electrode cell may be presented in conventional type or solid state coated wire types (Wang, 2006; Bakker *et al.*, 1999; Bucj, 1978; Abdullah *et al.*, 2010). Most ion-Selective Electrodes (ISEs) developed so far for determination of drugs are based on the use of ion-exchange systems. If the drug involves compounds containing organic cation, different salts are used for their conversion to an electrode-active ion-associate (Ngheim *et al.*, 2006; Koryta, 1977; Stefan *et al.*, 1997; Levenstam *et al.*, 2005; Youging *et al.*, 2006; Aly *et al.*, 2005; Nakatani *et al.*, 2005; Ma *et al.*, 2005).

The CWEs based on ion-associate quininium and Reineckate, phosphotungstate and phosphomolybdate were found to give useful results for determination of quinine in pharmaceuticals samples (Sekula *et al.*, 2006; Kobayashi *et al.*, 2010; Zareh *et al.*, 2001; Kamel and Sayour, 2009). In the reference method, the ISEs of the conventional type for quininium cation have been constructed and their performance characteristics studied (Shoukry *et al.*, 2007). The results were very satisfactory; however the preparation of the electrodes needs multiple steps. This is because all solid state electrodes of the coated wire type are much more easily prepared than the conventional type and have the advantage of not containing internal reference electrode. The present study describes a further search for a satisfactory PVC electrode for determination of Quininium cation based on different metals-coated wire electrodes.

Figure 1, shows the figure of quinine (Dewick, 2009), which is an alkaloid derived from the bark of the cinchona tree. It is a natural white crystalline alkaloid having antipyretic, antimalarial, analgesic and anti-inflammatory properties and a bitter taste. It is a stereoisomer of quinidine, which, unlike quinine, is an anti-arrhythmic. Several analytical methods have been developed for the quantitative determination of this

drug. These methodologies include chromatography (Samanidou *et al.*, 2005; 2004), spectrophotometry (Csernak *et al.*, 2006; Hassan, 2008; Tang *et al.*, 2005; Radhi *et al.*, 2010).

## MATERIALS AND METHODS

**Materials:** All chemicals used were of analytical grade. Polyvinyl chloride (PVC) of high molecular weight (Fluka). Dioctyl phthalate (Fluka), ammonium reineckate (Aldrich), phosphomolybdic acid (PMA) (Fluka) and Phosphotungstic Acid (PTA) (Fluka) were used. The Qn-containing tablets quininga (300 mg/tablet) are from Inga Pharma, Bombay. Sampling was carried out by grinding 10 tablets into fine powder, from which replicate samples were taken. All solutions and reagents were prepared in bi-distilled water. The Qn<sub>3</sub>PT and Qn<sub>3</sub>PM ion-associates and QnRn ion pair were prepared by a method similar to that previously described (Shoukry *et al.*, 1988). The elemental analysis of the produced ion-exchangers carried out at ANALAB, Faculty of Science, Kuwait University confirmed the stoichiometries: (1:1) (Qn: Rn), (3:1) (Qn:PT) and (3:1) (Qn:PM).

**Construction of the electrodes:** Spectroscopic pure silver or copper wires of 2.00 mm diameter and 12 cm length were tightly insulated by polyethylene tubes, leaving 1.0 cm at one end for coating and 0.5 cm at the other end for connection. The coating solution was prepared by dissolving 8.6, 8.6, or 11.0 mg of the ion-exchanger (QnRn, Qn<sub>3</sub>PT or Qn<sub>3</sub>PM, respectively), in 4 ml tetrahydrofuran, 104 mg of PVC and 102 mg of DOP were dissolved. Prior to coating, the polished silver or copper surface was washed with a detergent and water, thoroughly rinsed with deionized water and dried with acetone. Then, the wire was rinsed with chloroform and allowed to dry. Afterward, the wire was coated by quickly dipping it into the coating solution several times and allowing the film left on the wire to dry in air for about 2 min. The process was repeated three times until a plastic membrane of 1.00 mm thickness was formed. The prepared electrodes were preconditioned by soaking them for 1.5 h in  $10^{-3}$  M QnHCl solution (Shoukry *et al.*, 2007).

**Potentiometric studies and electrochemical systems:** Potentiometric measurements were carried out with an Orion, Model 420A pH/mV meter. A Caron circulator thermostat was used to control the temperature of the test solution.

The following electrochemical system was employed:

Ag|AgCl reference electrode| QnCl Test solution |Ag or Cu coated membrane | AgCl | Ag

**Construction of the calibration graphs:** Suitable increments of standard QnCl solution were added to 50 mL of  $10^{-6}$  M QnCl solution so as to cover the concentration range  $10^{-6}$  M- $1.7 \times 10^{-2}$  M. In this solution, the sensor and the reference electrode were immersed and the Electro-Motive Force (EMF) was recorded after 10 s, at 25°C for each addition.

**Life span of the electrodes:** The performance characteristics of the electrodes were investigated as a function of soaking time. For this purpose, the electrode was soaked in a solution with  $10^{-3}$  M in QnCl and the calibration graphs (pQn vs  $E_{mv}$ ) were constructed after 0.5, 1, 2 and 24 h.

**Effect of pH:** The pH of the test solution was altered by the addition of small volumes of HNO<sub>3</sub> and/or NaOH (0.1-1.0 M each). Graphs of (pH vs  $E_{mv}$ ) were plotted showing the effect of pH on different silver or copper coated wire electrodes of the different ion-exchangers.

**Selectivity:** The selectivity coefficients of the Qn-selective electrode, ( $K^{pot}_{Qn,j}$ ) towards different cationic species ( $j^{z+}$ ) were determined by the Separate Solution (SSM) (Cosofret, 1991) and Matched Potential (MPM) (Umezawa *et al.*, 1995).

**Analytical application:** The studied CWEs were used (by applying the standard addition method) to determine Qn<sub>2</sub>SO<sub>4</sub> in the pharmaceutical preparation, quininga tablets. In this method, small aliquots of a standard solution-0.1 M of QnCl-were added to the tablet sample solution; the ionic strength of the medium was kept constant at about 0.01 M with NaNO<sub>3</sub>. The difference in potential before and after the standard addition was used to calculate the sample solution content of Qn.

## RESULTS

**Life span of the electrodes:** The soaking of the electrode is important to form a hydrated gel layer at its surface and consequent good performance characteristics (Nernstian slope, response time 5 s and

low usable concentration range at 25°C). The CWEs were soaked in  $10^{-3}$  M QnCl solution and the calibration graphs of Ag- and Cu-wire electrodes for QnRn were plotted after 0.5, 1, 2 and 24 h (Fig. 2). It is clear from Table 1 that Ag-and Cu-CWEs exhibit good Nernstian performance characteristics. The soaking taking place up to 24 h for both types of electrodes has no effect on the calibration graph slope, except for with Cu-Qn<sub>3</sub>PM which has a short life span.

**Effect of pH:** The pH effect on the potential values of the electrode system of the quinine test solution was tested by the alteration of pH values using HNO<sub>3</sub> and/or NaOH within the range of pH2.00-11.00. Aliquots of 50.0 mL were transferred to a 100.0 mL titration cell and the tested ion-selective electrode in conjugation with an Ag/ AgCl reference electrode and a combined pH glass electrode being immersed in the same solution. The mV- readings were plotted against the pH-values for the quinine in Fig. 3. The electrode reading is constant whatever the pH value for the average range (3.2-7.6). In this range, the electrode can be used satisfactorily for Qn determinations in biological fluids.

**Selectivity:** The selectivity coefficients  $K^{pot}_{Qn,J^{z+}}$  of the CWEs for quininga pharmaceutical of quinine-respective drug towards the major serum cations (Schenk *et al.*, 2009; Asadi *et al.*, 2009), Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup> and Ca<sup>2+</sup> were determined by the Separate Solution Method (SSM) and matched potential (MPM) as described previously (Cosofret, 1991; Umezawa *et al.*, 1995), where the following equation was applied for (SSM):

$$\text{Log } K^{pot}_{Qn,J^{z+}} = E_2 - E_1/s + \log [Qn^+] - \log [J^{z+}]^{1/z}$$

where, Qn<sup>+</sup> is quininium cation; J<sup>z+</sup> is the interfering ion; E<sub>1</sub> and E<sub>2</sub> is the electrode potential in  $10^{-3}$  M solution of Qn<sup>+</sup> and J<sup>z+</sup>, respectively; and (s) is the slope of the calibration graph. The reciprocal value of the selectivity coefficient represents the minimum concentration ratio of the interfering ion to the primary ion at which interference start. Table 2 lists the mean selectivity coefficients of Qn-CWEs determined by both (SSM) and (MPM). The selectivity coefficients of the CWEs' values are very small (within maximum  $2.65 \times 10^{-2}$  to the minimum  $3.45 \times 10^{-4}$  for K<sup>+</sup> and Mg<sup>2+</sup>, respectively). Consequently, it will reflect no interference of the major serum cations. Multiplying

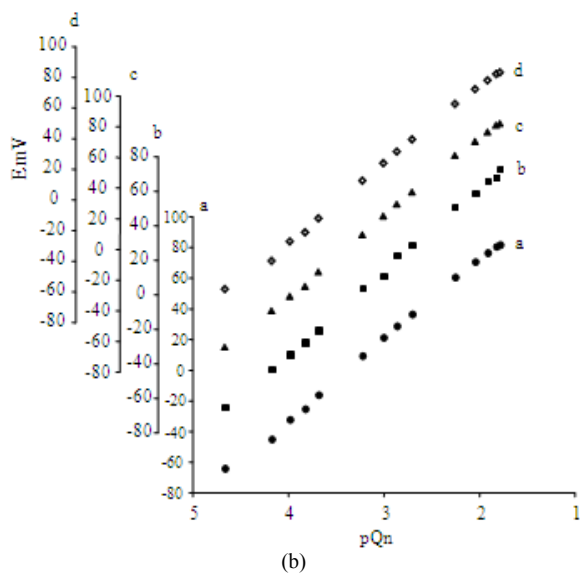
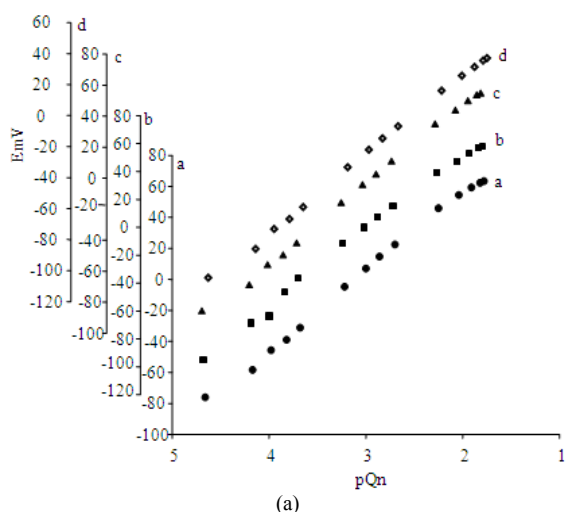


Fig. 2: Calibration graph obtained at 25°C after soaking Ag-QnRn (top) in 10<sup>-3</sup> M Qn<sup>+</sup>-solution for a: 0.5, b: 1, c: 2 and d: 24 hours and (below) Cu-QnRn

the selectivity coefficient by the concentration of the interfering ion produces the minimum concentration of the drug that can be detected in the blood serum without interference. Applying this mathematical treatment using the serum concentrations of the cations, it is evident that with down to 4.90×10<sup>-4</sup>, 1.96×10<sup>-5</sup>, 3.45×10<sup>-7</sup> and 8.04×10<sup>-5</sup> M Qn concentrations, in case of Ag-QnRn electrode and down to 4.00×10<sup>-4</sup>, 1.81×10<sup>-5</sup>, 2.88×10<sup>-6</sup> and 5.64×10<sup>-6</sup> M Qn concentrations, in case of Cu-QnRn electrode, no interference of Na<sup>+</sup>, K<sup>+</sup>, Mg<sup>2+</sup> and Ca<sup>2+</sup>, respectively, is expected. Homologous calculations of different Qn-CWEs are represented in Table 2.

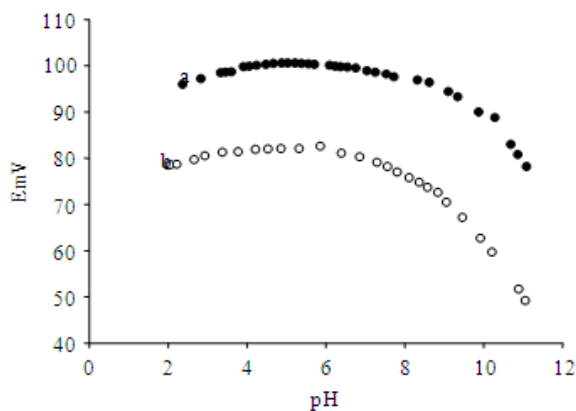


Fig. 3: Effect of pH of the test solution on the Qn<sup>+</sup> responsive electrode in (a) 1×10<sup>-3</sup> and (b) 1×10<sup>-4</sup> M solution at 25°C

**Analytical application:** From the results shown in Table 3, it is evident that the measurements in general exhibit low values of standard deviation (s), ranging from 0.64 when using Ag-Qn<sub>3</sub>PM to 1.45 when using Cu-QnRn for assaying tablets. The recovery values using Ag-CWEs were 100.9, 97.77 and 97.60 for Qn<sub>3</sub>PM, Qn<sub>3</sub>Pt and QnRn, respectively. The recovery values using Cu-CWEs were 93.30, 92.80 and 91.89 for QnRn, Qn<sub>3</sub>Pt and Qn<sub>3</sub>PM, respectively. The recovery values obtained for the analysis of Qn in the tablets reflect the high accuracy of the method.

## DISCUSSION

**Life span of the electrodes:** The soaking for up to 24 h for both types of electrodes has no effect on the calibration graph slope (Fig. 2). However, after 24 h soaking, the slope decreases gradually and the linear usable concentration range is greatly affected by soaking shown in Table 1. This may be attributed to gradual leaching of the electro active ion-exchanger from the membrane surface.

**Effect of pH:** Graphs of (pH vs E<sub>mV</sub>) show the same trends for all Qn-CWEs (Fig. 3). They have the shape of a plateau form in an average pH range from 3.2-7.6 and the pH decreased in both acidic and basic sides of the curve. This phenomenon allows the Qn-CWEs a good working range in blood serum since the pH of blood ranges from 7.35-7.45. For all Qn-CWEs, it is clear that at pH values extended to lower or higher values than the plateau ranges of the curves, the potential values decrease with decreasing and increasing the pH, respectively.

Table 1: Effect of soaking on the performance of Qn-electrodes

Ag-coated Qn responsive electrode			Cu-coated Qn responsive electrode		
Soaking time	Slope <sub>a</sub>	Concentration range (M)	Soaking time	Slope <sub>a</sub>	Concentration range (M)
-----4%QnRn-----			-----4%QnRn-----		
0.5 h	48.82	6.30×10 <sup>-5</sup> -1.70×10 <sup>-2</sup>	0.5 h	48.82	6.30×10 <sup>-5</sup> -1.70×10 <sup>-2</sup>
1 h	53.57	4.53×10 <sup>-5</sup> -1.60×10 <sup>-2</sup>	1 h	53.57	4.53×10 <sup>-5</sup> -1.60×10 <sup>-2</sup>
2 h	55.40	6.50×10 <sup>-5</sup> -1.78×10 <sup>-2</sup>	2 h	55.40	6.50×10 <sup>-5</sup> -1.78×10 <sup>-2</sup>
24 h	47.54	6.50×10 <sup>-5</sup> -1.65×10 <sup>-2</sup>	24 h	47.54	6.50×10 <sup>-5</sup> -1.65×10 <sup>-2</sup>
-----4%Qn3PT-----			-----4%Qn3PT-----		
0.5 h	53.50	1.78×10 <sup>-5</sup> -1.70×10 <sup>-2</sup>	0.5h	53.50	1.78×10 <sup>-5</sup> -1.70×10 <sup>-2</sup>
1 h	51.70	6.04×10 <sup>-5</sup> -1.54×10 <sup>-2</sup>	1 h	51.70	6.04×10 <sup>-5</sup> -1.54×10 <sup>-2</sup>
2 h	53.50	6.50×10 <sup>-5</sup> -1.65×10 <sup>-2</sup>	2 h	53.50	6.50×10 <sup>-5</sup> -1.65×10 <sup>-2</sup>
24 h	53.20	7.00×10 <sup>-5</sup> -1.65×10 <sup>-2</sup>	24 h	53.20	7.00×10 <sup>-5</sup> -1.65×10 <sup>-2</sup>
-----5%Qn3PM-----			-----5%Qn3PM-----		
0.5 h	51.25	2.20×10 <sup>-5</sup> -1.24×10 <sup>-2</sup>	0.5 h	51.25	2.20×10 <sup>-5</sup> -1.24×10 <sup>-2</sup>
1 h	52.33	4.58×10 <sup>-5</sup> -2.70×10 <sup>-2</sup>	1 h	52.33	4.58×10 <sup>-5</sup> -2.70×10 <sup>-2</sup>
2 h	52.64	6.50×10 <sup>-5</sup> -1.26×10 <sup>-2</sup>	2 h	52.64	6.50×10 <sup>-5</sup> -1.26×10 <sup>-2</sup>
24 h	53.01	1.00×10 <sup>-6</sup> -1.7×10 <sup>-2</sup>			

<sup>a</sup>mV/ Qn concentration decade

Table 2: Selectivity coefficients  $K_{Qn,J}^{pot}$  of Qn-responsive metal coated (Ag, Cu) electrodes

Interfering ion		Selectivity coefficient $K_{pot}^{Qn,Jz+}$			
Cation	Blood serum Level M	Mean value Ag	Mean value Cu	Ag	dMmin. Cu
Na+	0.14	<sup>a</sup> 3.53×10 <sup>-3</sup> <sup>b</sup> 2.30×10 <sup>-2</sup> <sup>c</sup> 2.25×10 <sup>-2</sup>	<sup>a</sup> 2.84×10 <sup>-3</sup> <sup>b</sup> 1.85×10 <sup>-2</sup> <sup>c</sup> 1.94×10 <sup>-2</sup>	<sup>a</sup> 4.90×10 <sup>-4</sup> <sup>b</sup> 3.22×10 <sup>-3</sup> <sup>c</sup> 3.15×10 <sup>-3</sup>	<sup>a</sup> 4.00×10 <sup>-4</sup> <sup>b</sup> 2.60×10 <sup>-3</sup> <sup>c</sup> 2.72×10 <sup>-3</sup>
K+	0.005	<sup>a</sup> 3.92×10 <sup>-3</sup> <sup>b</sup> 3.72×10 <sup>-2</sup> <sup>c</sup> 2.65×10 <sup>-2</sup>	<sup>a</sup> 3.62×10 <sup>-3</sup> <sup>b</sup> 2.05×10 <sup>-2</sup> <sup>c</sup> 1.86×10 <sup>-2</sup>	<sup>a</sup> 1.96×10 <sup>-5</sup> <sup>b</sup> 1.86×10 <sup>-3</sup> <sup>c</sup> 1.33×10 <sup>-4</sup>	<sup>a</sup> 1.81×10 <sup>-5</sup> <sup>b</sup> 1.03×10 <sup>-4</sup> <sup>c</sup> 9.30×10 <sup>-5</sup>
Mg2+	0.001	<sup>a</sup> 3.45×10 <sup>-4</sup> <sup>b</sup> 2.23×10 <sup>-3</sup> <sup>c</sup> 1.82×10 <sup>-3</sup>	<sup>a</sup> 2.88×10 <sup>-3</sup> <sup>b</sup> 1.68×10 <sup>-2</sup> <sup>c</sup> 1.38×10 <sup>-2</sup>	<sup>a</sup> 3.45×10 <sup>-7</sup> <sup>b</sup> 2.23×10 <sup>-6</sup> <sup>c</sup> 1.82×10 <sup>-6</sup>	<sup>a</sup> 2.88×10 <sup>-6</sup> <sup>b</sup> 1.68×10 <sup>-5</sup> <sup>c</sup> 1.38×10 <sup>-5</sup>
Ca2+	0.003	<sup>a</sup> 2.68×10 <sup>-4</sup> <sup>b</sup> 2.75×10 <sup>-3</sup> <sup>c</sup> 1.83×10 <sup>-3</sup>	<sup>a</sup> 1.88×10 <sup>-3</sup> <sup>b</sup> 1.47×10 <sup>-2</sup> <sup>c</sup> 1.35×10 <sup>-2</sup>	<sup>a</sup> 8.04×10 <sup>-7</sup> <sup>b</sup> 8.25×10 <sup>-6</sup> <sup>c</sup> 5.50×10 <sup>-6</sup>	<sup>a</sup> 5.64×10 <sup>-6</sup> <sup>b</sup> 4.41×10 <sup>-5</sup> <sup>c</sup> 4.05×10 <sup>-5</sup>

<sup>a</sup>: QnRn; <sup>b</sup>: Qn<sub>3</sub>PT; <sup>c</sup>: Qn<sub>3</sub>PM; <sup>d</sup>: Minimum concentration of drug detected in blood serum without interference

Table 3: Applying three different Qn-responsive electrodes to the determination of Qn in the pharmaceutical tablets, Quininga, using the standard addition method

Ion exchanger	Labeled amount (mg)	Amount found (mg) <sup>a</sup>		Reference method (Shoukry <i>et al.</i> , 2007)	(% ) Recovery <sup>b</sup>		Reference method (Shoukry <i>et al.</i> , 2007)
		Ag	Cu		Ag	Cu	
QnRn	78.29	76.34±1.02 F =2.7 t =17.55	73.04±1.45 F =1.37 t =6.22	79.87±1.70	97.60±1.30	93.30±1.86	102.00
Qn3PT	78.29	76.52±0.65 F =16.5 t =2.45	72.66±0.67 F =17.54 t =3.3	76.11±0.16	97.77±0.87	92.80±0.84	97.22
Qn3PM	78.29	79.04±0.639 F =7.08 t =0.76	71.94±0.73 F =5.423 t =7.6	79.79±1.70	100.9±0.82	91.89±0.93	101.90

<sup>a</sup>Mean ±standard deviation of five determinations, the t- and F- test values refer to comparison of the proposed method with the reference method of four determinations. Theoretical values of 95% confidence limit,  $F_{(4,3)} = 9.12$ ,  $F_{(3,4)} = 6.59$ ,  $t_7 = 2.36$ , <sup>b</sup>After adding different amounts of the pure labeled to the pharmaceutical formulations, each value is an average of five determinations

The decrease in potential at the acidic side of the curves is most probably due to nitrate ion interface. On the other hand, the decrease in potential at the basic side of

the curve is attributed to the decrease of quinone cationic species (Qn<sup>+</sup>) as a result of releasing the free base from the pharmaceutical compound.

**Selectivity:** The selectivity of an ion pair complex-based membrane depends on the ion exchange process at the membrane test interface and the mobility of the respective ions in the membrane. None of the investigated ions was found to interfere due to small values of the selectivity coefficients in Table 2. The minimum molarities of the drug detected in blood serum without interference by Qn-CWEs were mostly of a micro-scale, except for with  $\text{Na}^+$  cation. This shows that both Ag- and Cu-CWEs are so selective for quininium that they can be used conveniently in the determination of quininium in the pharmaceutical preparations and biological fluids.

**Analytical application:** The statistical t- and F-tests were used to analyze the data in Table 3, starting from calculating the mean and the standard deviation of each determination for the applied Ag- and Cu-CWEs. The results show that the present CWEs of Ag and Cu are highly accurate (as shown by the recovery values) and highly precise (as revealed by the corresponding standard deviations).

To compare the efficiency of the two metal electrodes with respect to the reference method, the t- and F-test were applied. In making a significant test we are testing the truth of a hypothesis which is known as a null hypothesis, often denoted by  $H_0$ . The term null is used to imply that there is no difference between the mean,  $\bar{x}$  and the true values,  $\mu$ , of the proposed and reference values ( $\mu_1 = \mu_2$ ). In other words, we need to test whether  $\bar{x}_1$  and  $\bar{x}_2$  differ significantly from zero by the application of a t-test. The calculated |t| values of Ag-QnRn, Cu-QnRn, Ag-Qn<sub>3</sub>PT, Cu-Qn<sub>3</sub>PT and Cu-Qn<sub>3</sub>PM are each higher than the critical value  $t_7 = 2.36$ . Accordingly, the difference between the two results of the reference and the proposed methods is significant at 5 % level and the null hypothesis is rejected. In fact, since the critical value of  $t_7$  for 0.01 is about 3.5, the difference is significant at 1 % level except for Ag-Qn<sub>3</sub>PT. In other words, if the null hypothesis is true, then the probability of such a large difference arising by chance is less than 1%. The Ag-Qn<sub>3</sub>PM calculated value ( $t_7 = 0.76$ ) is less than the critical value ( $t_7 = 2.36$ ), so the null hypothesis is retained and there is no evidence that using the conventional or Ag-CWE affects the recovery.

Another significance test that describes the precisions of the proposed method with a reference method is the F-test. The F-test is used for comparing whether the difference between two sample variances is significant (i.e., to test  $H_0: \sigma_1^2 = \sigma_2^2$ ). If the null hypothesis is true, then the variance ratio should be close to 1. The F-values calculated were 2.7, 1.37 and

5.423 for Ag-QnRn, Cu-QnRn and Cu-Qn<sub>3</sub>PM, respectively, which are less than Critical  $F_{(3, 4)}$  (6.59). Since the calculated values are less than the critical values of F, the variance of the proposed method is significantly greater than that of the reference method at 5% probability level (i.e., the reference method is more precise). Comparatively, Ag-Qn<sub>3</sub>PM calculated  $F_{(3, 4)}$  (7.08) is higher than critical  $F_{(3,4)}$  (6.59), which means that the Ag-Qn<sub>3</sub>PM is more precise than the reference method. Conversely, the calculated  $F_{(4, 3)}$  values were found to be 16.5 and 17.54 for Ag-Qn<sub>3</sub>PT and Cu-Qn<sub>3</sub>PT, respectively. The calculated values were higher than critical  $F_{(4, 3)}$  (9.12), which mean that (in case of Qn<sub>3</sub>PT) the reference method is more precise than with Cu-Qn<sub>3</sub>PT or Ag-Qn<sub>3</sub>PT.

## CONCLUSION

The ion pair QnRn and the ion associates Qn<sub>3</sub>PT and Qn<sub>3</sub>PM are efficient ion exchangers for the construction of Qn-CWEs. Such electrodes can be successfully used for the micro determination of Qn<sub>2</sub>SO<sub>4</sub> in its pharmaceutical preparation. The chemometric study concludes that the reference method is usually more than the proposed method except for Ag-Qn<sub>3</sub>PM. In general, Ag-Qn<sub>3</sub>PM CWE showed a discrete behavior regarding accuracy and silver metal preference.

## ACKNOWLEDGEMENT

The cooperation of Kuwait University-College of Science through the facilities of Analytical Laboratory (ANALAB) with The Public Authority for Applied Education and Training in the integration of the scientific research.

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