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# Determination of haloperidol drug in ampoules and in urine samples using a potentiometric modified carbon paste electrode

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ABSTRACT

A modified carbon paste electrode for haloperidol drug based on haloperidol-phosphomolybdate (HP-PM) as an ion-exchanger dissolved in plasticizer DBP and its potentiometric characteristics were discussed. The electrode exhibited a good Nernstian slope of 56.9 ± 0.3 mV/decade with a linear concentration range from $3.2 \times 10^{-6}$ to $1.0 \times 10^{-2}$ M for the haloperidol ion. The limit of detection (LOD) was $1.5 \times 10^{-6}$ M. It had response time of 5–8 seconds (s), useable in pH range of 6.2–8.6 and temperature of 20–60 °C. The electrode shows clear discrimination of haloperidol drug from several inorganic ions, sugars and some common drug excipients. The sensor was applied for determination of haloperidol drug in urine and in pharmaceutical formulations using potentiometric determination, standard addition and the calibration curve methods. The results are satisfactory with excellent percentage recovery comparable or better than those obtained by other routine methods.



## 1. Introduction

Haloperidol (HP) is useful in the treatment of many psychotic disorders such as hyperactivity, agitation, Schizophrenia and mania as well as in the treatment of neurological disorders such as Gilles de la Tourette syndrome, Huntington's chorea and acute/chronic brain syndrome. However, haloperidol produces extrapyramidal side effects including acute dystonic reactions, acathisia syndrome, drug induced parkinsonism, bradykinesia and tardive dyskinesia. The IUPAC name of haloperidol is 4-[4-(4-chlorophenyl)-4-hydroxypiperidin-1-yl]-1-(4-fluorophenyl)butan-1-one. As a tertiary amine with p*K*a of 8.3, it is soluble in organic solvents. HP is a white or almost white powder, melting point of 150–153 °C [1–3]. Excipients such as lactic acid and water are added to formulate the drug for injection. The empirical formula for haloperidol is $C_{21}H_{23}ClFNO_3$ as shown in Fig. 1. In view of its therapeutic importance, attempts to develop a sensitive analytical method for assay of haloperidol in pharmaceutical preparations and urine sample were performed. These comprise gas chromatography (GC), gas chromatography–mass spectrometry (GC–MS), reverse phase high performance liquid chromatography (RP-HPLC), high-performance liquid chromatography (HPLC), high performance liquid chromatography mass spectrometer (HPLC–MS), capillary electrophoresis [3–9], UV/Vis spectrophotometry [1,10] and voltammetric analysis [11–13]. These methods are highly sensitive. However, they are very expensive as they entail tedious sample manipulation, long analysis time as well as complex instrument setup hence becoming unsuitable for routine analysis. Consequently, there is a need for devising a selective, fast, accurate and inexpensive tool for determination of haloperidol drug.

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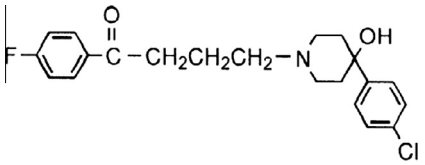


**Fig. 1.** The chemical structure of Haloperidol.

Potentiometric methods with ion-selective electrodes (ISEs) are effective in the analysis of drugs in real samples for their advantages of simple fabrication, good selectivity, short response time, applicability to miscellaneous solutions and possible automation [14–16]. Therefore, ISEs are more desirable alternatives.

Since 1970s, carbon paste electrodes have become widely popular electrode sensors. Chemically modified carbon paste electrodes, CMCPEs are advantageous for ease of preparation and very stable response as well as very low Ohmic resistance [17] which make CMCPEs especially promising [18–20].

With these merits in mind, it is desirable to fabricate a modified carbon paste electrode for haloperidol. This manuscript describes the work toward this end. That is we have devised an electrode that comprises haloperidol-phosphomolybdate as the ion-exchanger dissolved in dibutyl phthalate (DBP). The present electrode has notable characteristics: near-Nernstian slope, low detection limit, wide concentration range, short response time and applicability in ampoule and urine samples.

## 2. Experimental

### 2.1. Reagents

Doubly distilled water was used throughout all experiments. Haloperidol and pharmaceutical preparation (Ampoules 5 mg/mL)were provided by the General Administration of Pharmacy Ministry of Health (Gaza-Palestine). The ampoule contains lactic acid and water for injection. Graphite powder, silicotungstic acid (STA) $H_4[SiW_{12}O_{40}]$, silicomolybdic acid (SMA) $H_4[SiMo_{12}O_{40}]$, phosphotungstic acid (PTA) $H_3[PW_{12}O_{40}]$, phosphomolybdic acid (PMA) $H_3[PMo_{12}O_{40}]$ and sodium tetraphenylborate (Na-TPB) $Na[C_{24}H_{20}B]$, dibutyl phthalate (DBP),dioctyl phthalate (DOP), tris(2-ethylhexyl) phosphate (DOPh) and dioctylsebacate (DOS)were from Sigma–Aldrich (CH-9471 Buchs-Germany). In addition, glucose, galactose, fructose, sucrose, artane and tramadol were obtained from local drug stores. Other salts were commercially available.

### 2.2. Apparatus

A saturated calomel electrode (SCE) was used as reference electrode and was obtained from Sigma–Aldrich Co. (St Louis, MO, USA). Potentiometric and pH measurements were performed using a Pocket pH/mV meters, (pH315i) from Wissenschaftlich-Technische Werkstatten GmbH (WTW), Weilheim, Germany. Emf measurements with CPE were carried out with the following cell assemblies: Hg, $Hg_2Cl_2$ (s), KCl(sat.) || sample solution || carbon paste electrode.

The performance of the electrodes were investigated by measuring the emfs of HP solutions having concentrations ranging $1.0 \times 10^{-7}$–$10 \times 1.0^{-2}$ M by serial dilution. Each solution was stirred and the potential reading was recorded after 2–3 min and plotted as a logarithmic function of HP ion activities.

### 2.3. Synthesis of ion-exchangers

Several ion-exchangers, namely haloperidol silicotungstate ($HP_4$-ST), silicomolybdate ($HP_4$-SM), phosphotungstate ($HP_3$-PT), phosphomolybdate ($HP_3$-PM) and tetraphenylborate (HP-TPB) were made by mixing a hot solution of 100 mL of $10^{-2}$ M haloperidol drug and equivalent amounts of STA, SMA, PTA, PMA or Na-TPB($10^{-2}$ M). The products that formed were collected, intimately washed, dried and pulverized for making the sensors of HP ion.

### 2.4. Preparation of modified carbon paste electrode

Carbon paste electrodes were made as described previously [21,17]. Graphite, ion-exchanger and selected plasticizers were intimately mixed in a Petri dish to a fine paste. Some of the paste was packed firmly into the end of a disposable polypropylene syringe (ca. 3 mm i.d. and 6 cm long). Electrical contact was secured through a copper wire screw. The outer layer of the carbon paste was scraped and the surface of the electrode was polished before each set of measurements. The sensor was used directly without preconditioning.

### 2.5. Interferences

The influence of some inorganic and organic cations, sugars and some excipients or additives on the proposed ISE were investigated. The matched potential method (MPM) [22,23] was employed sinceit is independent of the Nicolsky–Eisenman equation, or any of its modifications. This method was recommended in 2000 by IUPAC as a method that gives analytically relevant practical selectivity coefficient values. According to this method, the activity of (HP) was increased from $a_A = 1.0 \times 10^{-5}$ M (reference solution) to $a'_A = 5.0 \times 10^{-5}$ M and the change in potential ($\Delta E$) corresponding to this increase were measured. Furthermore, a solution of potentially interfering ions of concentration $a_B$ in the range $1.0 \times 10^{-1}$–$1.0 \times 10^{-2}$ M is added to a fresh $1.0 \times 10^{-5}$ M (reference solution) until the same potential change ($\Delta E$) was recorded. The selectivity factors, were then evaluated using the following equation:

$$K^{MPM}_{A,B} = \frac{(a'_A - a_A)}{a_B}$$

In the separate solution method SSM [22,23], the potential of a cell utilizing a working electrode and a reference electrode is measured in a solution of the HP ions, $E_1$, and the other of the interferent ions (J), $E_2$. The selectivity coefficient was calculated using the following equation: