Egypt. J. Anal. Chem., Vol. 16, pp 47-58 (2007)

Carbon Paste Ion–Selective Electrode for the Determination of Metoclopramide

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Summary- Metoclopramide C-paste ion-selective electrode based on metoclopramide–tetraphenylborate has been prepared. A Nernstian response is shown by this electrode within $4x10^{-6}$–$3.1x10^{-3}$ M concentration range. The change of pH within the range (3-5.5) does not affect the electrode performance. The standard electrode potentials, E^o, were determined at different temperatures and used to calculate the isothermal temperature coefficient of the electrode. The electrode shows good selectivity with respect to many inorganic cations, sugars and amino acids. Metoclopramide is determined successfully in pure solution and in pharmaceutical preparation using standard addition, and potentiometric titration methods and flow injection analysis technique (FIA).

Introduction

Metoclopramide hydrochloride (MDCl) is an anti-naused and anti-vomiting agent. For control purposes, it is important to have sensitive and reliable analytical methods.

Several methods have been reported for the determination of metoclopramide hydrochloride including high performance liquid chromatography[1,2], thin layer chromatography[3], capillary electrophoresis[4], spectrophotometery[5], fluorimetric estimation[6] and electrometric determination[7].

In the present work, metoclopramide C-paste ion-selective electrode is constructed and its performance characteristics are investigated[8]. The electrode is based on incorporation of the metoclopramide-tetraphenylborate

(MD-TPB) ion-pair associate in a C-paste plasticized with dibutylphthalate (DBP). The electrode is used successfully as a sensor to determine metoclopramide in pure solution and in pharmaceutical preparations

Experimental

Reagents and materials

All reagents used throughout the work were of analytical-reagent grade and solutions were made with bidistilled water. Metoclopramide hydrochloride (MDCl) was provided by (RAMIDA) Pharmaceutical Chemical Company, Egypt. Sodium tetraphenylborate (NaTPB) $Na[B(C_6H_5)_4]$, dibutylphthalate (DBP) (Fluka), Stock concentrated solutions (0.1 M) of MDCl was prepared by dissolving the accurately weighed amounts of the pure compound (3.543 g) in 100 ml of bidistilled water. Dilute solutions were prepared by appropriate dilutions.

The test drug sample: Primperan tablets (10 mg) provided by Delagrange (Paris) were analysed for MDCl.

Preparation of the ion-exchanger

The ion-exchanger with the tentative formula MD-TPB was prepared by mixing one volume of 10^{-2} M MDCl with one volume of 10^{-2} M TPB.

The resulting precipitate was left in contact with its mother liquor over night to assure complete coagulation, then, the precipitate was filtered and washed thoroughly with distilled water till chloride free (tested using $AgNO_3$ solution) and left to dry at room temperature for at least 48 hour.

The suggested tentative formula and purity of ion-exchanger was checked by elemental analysis for carbon, hydrogen and nitrogen, at the micro analytical centre, Cairo University, table (1).

Table (1): Elemental analysis of the ion-exchanger $(C_{14}H_{22}N_3O_2[B(C_6H_5)_4]$.

	C%		H%		N%	
Ion-pair	Calculated	Found	Calculated	Found	Calculated	Found
MD-TPB	73.72	72.62	6.84	6.98	6.78	6.60

Preparation of the working electorde

Carbon paste was prepared by thoroughly mixing the precipitated ion-associates MD-TPB with graphite powder CR5 (Tesla lanskroun) and di-butylphthalate DBP (Fluka) in the ratios of 5 : 47.5 : 47.5, respectively using agate pestle and mortar. This mixture was packed into the piston-like electrode Holder with an active surface diameter of 3 mm.

No special pretreatment of the prepared electrodes was used except for a routine surface renewing by removing a thin layer of the used paste by a wet filter paper. The easy and very cheap preparation of CPE and no risk of mechanical damage of the electrode material is very advantageous.

Apparatus

Potentiometric and pH measurements were carried out using a SEIBOLD G-103 digital pH/mV meter (Vienna, Austria). A Techne Circulator Thermostat C-100, was used to control the temperature of the test solution. A saturated calomel electrode (SCE) (model B 351) was used as a reference electrode.

The FIA system

The flow injection setup was composed of a 4 channel peristaltic pump (Ismatec, ISM 827), (Zurich, Switzerland), injection valve model 5020 with exchangeable sample loop from Rheodyne (Cotati, CA, USA). The electrodes were connected to WTW micro-processor pH/ion meter pMX 2000 (Weilheim, Germany) and interfaced to a strip shart recorder model BD111 from Kipp and Zonn (Deflt, Netherlands).

The C-paste ion-selective electrode with flow cup, reference electrode (SCE) and the outlet tube were placed in a beaker, where the level of sloution was kept 1 cm above the electrode surface.

Selectivity of the electrode

selectivity coefficient was determined by the separate solution method[9] in which the following equation was applied:

$$\log K^{Pot}_{drug,J^{z+}} = (E_2 - E_1)/S + \log[drug] - \log\left[J^{z+}\right]^{1/z}$$

Where E_1 is the electrode potential in 10^{-3} M MDCl solution, E_2 is the potential in 10^{-3} M solution of the interfering ion (J^{Z+}), and S is the slope of the calibration graph.

The tolerance of the electrodes towards the amino acids and sugars has been calculated by adding small increments of 1 M interfering species to 50 ml of 10^{-5} M MDCl solution. The tolerance was considered as the concentration imparting a 2 mV drift in the potential reading.

In FIA, a series of standard MDCl sloutions of concentration 10^{-5}-10^{-2} M was prepared, its corresponding peak heights were measured and then solutions that is 10^{-2} M of interferents were measured at the same conditions and their peak heights were compared to those obtained from the standard series.

Potentiometric determination

The standard addition method was applied[10], in which known increments of 10^{-2} M MDCl solution were added to 50 ml water containing 10-100 mg of the investigated drug. The change in mV reading was recorded for each increment and used to calculate the concentration of the MDCl sample solution.

In FIA, a series of standard MDCl solutions and another for the pharmaceutical preparations of the same concentrations were also prepared. The obtained peak heights were compared to those of the standard series and the recovery can be calculated as the ratio between the peak height of the sample and that of its corresponding concentration.

Potentiometric titrations

Different weights of the investigated compound have been transferred into 100 ml titration cell and diluted to 50 ml by distilled water. The resulting solutions were titrated using 10^{-2} M solution of PTA at 25±0.1^{o}C.

Results and discussion

Composition of paste and electrode performance

The amount of lipophilic salt should be sufficient to obtain reasonable ionic exchange at the paste-test solution interface which is

responsible for the electrode potential. The composition of the paste was varied so as to reach the optimum composition. An electrode modified by 5%(W/W) of MD-TPB with 47.5% DBP as plasticizer has a slope of 63±2 mV/concentration decade and a wide range of linearity, amounting to $4x10^{-6}$-$3.1x10^{-3}$ M.

In flow measurements the dependence is semi-logarithmic over a wide analyte activity range according to the Nickolsky-Eisenman equation. So the main favorable feature of this detection is the high response of the C-paste electrode potential to concentration change.

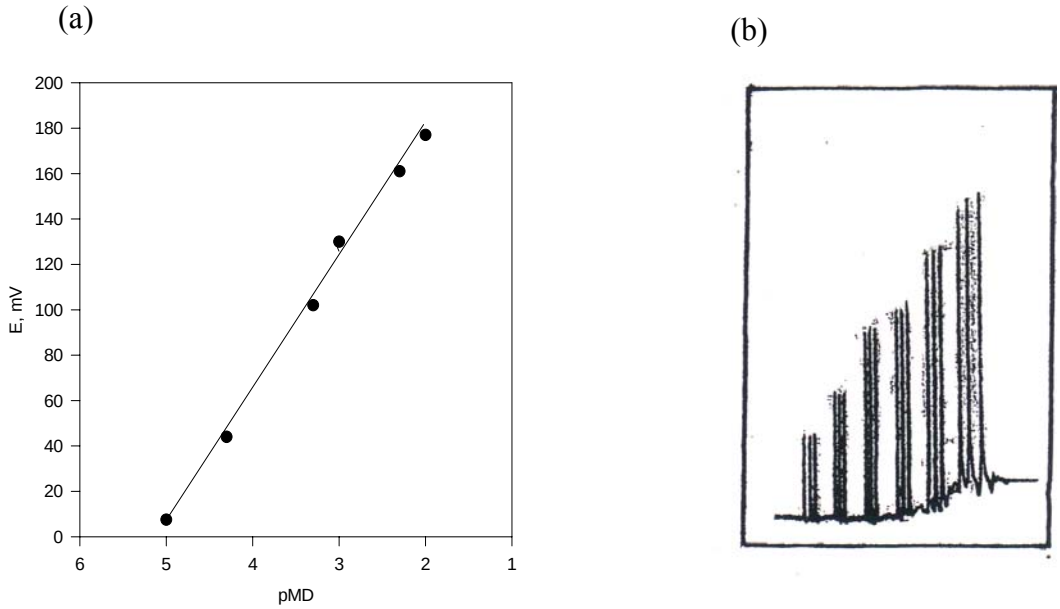

Fig. (1): The calibration graphs (a) and its corresponding recordings (b) obtained for MD-TPB electrode at optimum FIA conditions.

The slope of the calibration graph is 61 (FIA) compared to 63 mV/decade (batch) for MD-TPB electrode.

Effect of pH

The pH of the test solution (10^{-3} , $5x10^{-4}$ and 10^{-4} M) of MDCl was varied gradually and the respective MD-TPB electrode potential readings were measured as a function of pH.

As shown by (Fig. 2), the change in pH does not affect the potential readings within the pH range (3-5.5) for (10^{-3} , $5x10^{-4}$ and 10^{-4} M MDCl) test solution

In these pH ranges, the electrodes can be used safely for the respective determination. At pH value less than 3.0, the potential decreases which may be attributed to the penetration of chloride ion into the paste surface or due to formation of the diprotonated species $(HMD)^{2+}$. At pH higher than 5.5, it is expected that the protonated species starts to be neutralized, and hence decreases yet, the potential readings increase and increase markedly in the alkaline solutions. The increase in potential reading is most probably attributed either to the penetration of Na^+ ions into the paste surface or changes in liquid-junction potential.

For FIA measurements, the effect of pH of the test solution on the electrode potentials was studied in two ways either by preparing a series of solutions of concentration that is 10^{-2} M MDCl and pH ranging from 2.0-10.0 which are then injected in the flow stream and the peak heights, representing variation of potential response with pH, were recorded, the results show that the change of pH does not affect the peak hights within the pH ranges mentioned above.

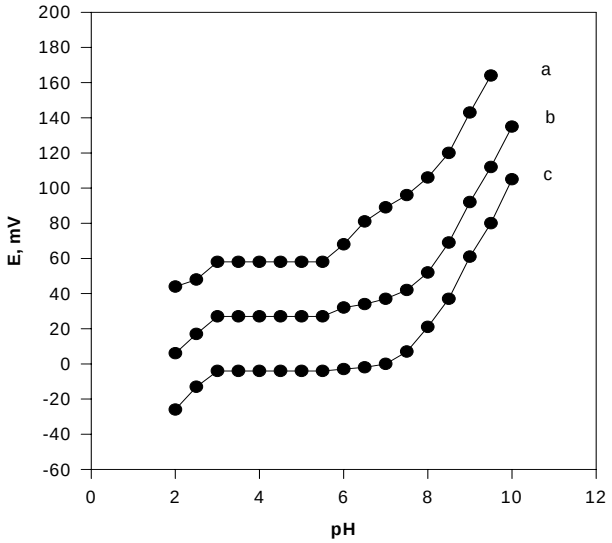

Fig. 2. Effect of pH of the test solution of concentrations 10^{-3} M (a), $5x10^{-4}$ M (b),10^{-4} M (c) MDCl on the Potential response of MD-TPB electrode.

Selectivity of the electrode

The selectivity of the ion-pair based paste electrodes depends on the selectivity of the ion-exchange process at the paste-test solution interface and

the mobilities of the respective ions in the paste. The data presented indicate that the MD-TPB electrode is highly selective for MDCl (Table 2). The inorganic cations do not interfere, this may be due to the differences in their ionic size, mobility and permeability as compared to that of MD^+ cations. In case of amino acid and sugars, the high selectivity is mainly attributed to the difference in polarity and the lipophilic nature of their molecules relative to that of MD^+ species.

It was shown earlier for solid state membrane electrodes, that the apparent (or conditional) selectivity coefficient measured in transient flow injection conditions may differ significantly from that measured in batch conditions[11,12], Therefore, in FIA measurements, where sample remains incontact with the electrode for a short period of time, the apparent selectivity of the membrane should be different from that found in batch conditions.

Table (2): Selectivity coefficients and tolerance values for the MD-TPB responsive electrode.

$-\log K^{Pot}_{MD, J^{z+}}$					
Interferent	Batch	FIA	Interferent	Batch	FIA
Na^+	2.55	1.66	Cr^{3+}	4.76	1.01
NH_4^+	2.92	2.33	Zn^{2+}	3.69	1.66
Ni^{2+}	3.82	1.02	Co^{2+}	3.76	1.75
Mg^{2+}	3.85	1.45	Ba^{2+}	3.79	1.52
Cu^{2+}	3.20	1.05	Sr^{2+}	3.63	1.05
Mn^{2+}	4.30	1.10	Pb^{2+}	4.32	1.03
Al^{3+}	4.69	1.10			

Interferent	Tolerance
Lactose	703
Glucose	No interference
Maltose	No interference
Fructose	No interference
Glycine	No interference

Effect of temperature of the test solution

Calibration graphs were constructed at test solution-temperatures covering the range between 25-60 ^{o}C for the electrode. The slope, usable concentration range, $E^{o}_{elec.}$ and response time of the electrode are given in table (3) showing that MD-TPB electrode have a good nernstian behaviour in the temperature ranges 25-60 ^{o}C.

Plots of E^{o} versus (t-25) ^{o}C are straight lines, (figure 4) the slope of which is the isothermal temperature coefficient of the electrode amounting to $6.7x10^{-4}$ V/^{o}C For MD-TPB electrode .

The isothermal temperature coefficient (dE^{o}/dt) was determined at different temperatures using the following equation

$$E^{o}_{elec.} = E^{o}_{25} + (dE^{o}/dt)\,(t-25)$$

The standard electrode potential $E^{o}_{elec.}$ was Calculated using the following equation

$$E^{o}_{cell} + E^{o}_{reference} = E^{o}_{electrode}$$

E^{o}_{cell} was determined from the calibration curves (Fig. 3) as the intercepts of these graphs at – log[pMD] = 0.

Table 3: Performance characteristics of MD-TPB carbon paste electrodes at different temperatures

Temperature (^{o}C)	Slope mV/decade	Usable concentration Range (M)	E^{o}_{cell} (mV)	$E^{o}_{elec.}$ (mV)	Response Time(s)
25	61	$4x10^{-6} – 2.1x10^{-3}$	290	534	< 10
30	63	$4x10^{-6} – 2.1x10^{-3}$	292	533	< 10
35	66	$4x10^{-6} – 1.5x10^{-3}$	310	548	< 10
40	68	$4x10^{-6} – 1.5x10^{-3}$	315	549	< 10
45	69	$4x10^{-6} – 1.5x10^{-3}$	317	548	< 10
50	70	$4x10^{-6} – 1.5x10^{-3}$	326	554	< 10
60	77	$4x10^{-6} – 1.5x10^{-3}$	335	556	< 10

Isothermal coefficient = 0.000677 V/^{o}C.

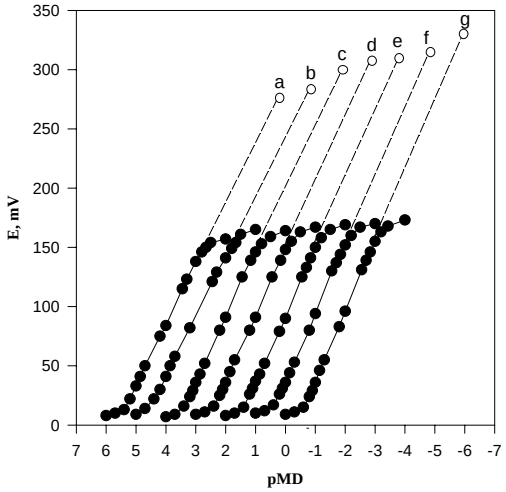

Fig. 3. Calibration curves of MD-TPB electrode at test solution temperatures 25 (a), 30 (b), 35 (c), 40 (d), 45 (e),50 (f) and 60 ^{o}C (g).
Note: All curves start at pMD = 6

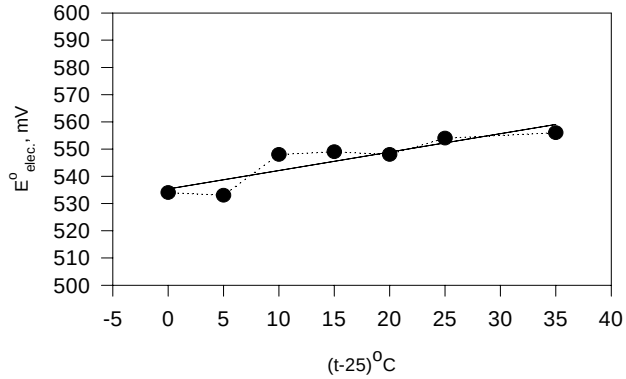

Fig. 4. Variation of $E^{o}_{elec.}$ of MD-TPB electrode with temperature.

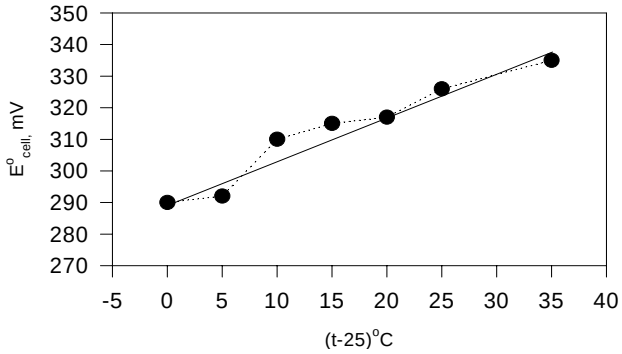

Fig. 5. Variation of E^{o}_{cell} of MD-TPB electrode with temperature

Temperature coefficient of the cell is also important as it represents the practical influence of temperature on measuring potential and the same method was applied.

Analytical applications

Determination of MDCl

The electrodes proved to be useful for the determination of MDCl by the standard addition method and by potentiometric titration in pure solutions and in pharmaceutical preparations. Collective results, given in table (4), indicate the high accuracy and precision of the present work as compared to those previously reported[2,7] depending on more complicated instrumentations or time-consuming pretreatment steps, while the combination of sensitivity, selectivity and simplicity of ion–selective electrode potentiometry makes it an excellent and versatile technique .

The performance of the method was assessed by calculation of the *t*- and *F*-values in comparison to the published method[13]. Mean values were obtained in a studentś *t*– and *F*– test at 95% confidence limits for five degrees of freedom[14], and the results showed that the calculated *t*- and *F*- values did not exceed the theoretical values, table (5).

In FIA conditions, the peak heights comparison is the best method used for the drugs determination in its pure state or pharmaceutical preparations, where the peaks obtained from series of different concentrations of the studied drug are compared with those obtained by a standard series of the drug measured under the same conditions, flow rate, sample volume, pH and temperature. The % recovery can be obtained as the ratio of the peak heights and thus the concentrations can be calculated.

Table (4): Determination of MDCl applying MD-TPB responsive electrode

Sample	Standard Addition Method			Potentiometric Titration			under FIA conditions		
	Taken[2] (mg)	Found (mg)	recovery (%)	Taken[2] (mg)	Found (mg)	recovery (%)	Taken[2] (mg)	Found (mg)	recovery (%)
Pure Solution	0.17	0.17	100.00	31.90	32.04	100.43	1.77	1.76	99.43
	1.77	1.78	99.80	42.50	43.16	101.55	17.71	17.65	99.66
	17.70	17.70	98.60	53.10	53.96	101.62	88.57	89.19	100.70
	MR[3]± SD[1] 100.2±0.4			MR[3]±SD[1] 101.2±1.0			MR[3]± SD[1] 99.9±0.6		
Metoclo-pramide tablet	2.20	2.19	97.70	31.90	31.87	99.90	1.77	1.77	100.00
	22.14	21.81	99.30	42.50	43.20	101.65	17.71	17.46	98.64
	221.43	221.40	99.00	53.10	53.70	101.13	88.57	85.91	97.00
	MR[3]± SD[1] 99.2±0.8			MR[3]± SD[1] 100.9±1.2			MR[3]± SD[1] 98.5±1.5		

1. Standard deviation (three determinations).
2. Taken mg per 50 ml.
3. Mean recovery

Table (5): Statistical treatment of the results obtained by MD-TPB electrode in comparison with official method.

	Official method	Standard addition method	Potentiometric titration	FIA
Pure solution				
X ± S.D	101.1±0.57	100.3±0.4	101.2±1.0	100±0.61
t value (3.707)*		2.30	0.17	2.60
$f^{3,3}$ value (9.27)**		2.03	3.07	1.14
Primperan(tablets)				
X ± S.D.	98.76±0.92	99.4±0.8	100.9±1.2	98.5±1.5
t value (3.707)*		1.05	2.82	0.29
$f^{3,3}$ value(9.27)**		1.32	1.70	2.66

*probability level 95% ** one tail critical F value. S.D: Standard deviation

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