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PVC matrix membrane sensor for potentiometric determination of metoclopramide hydrochloride in some pharmaceutical formulations

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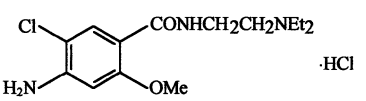
Abstract

The construction and characteristic performance of metoclopramide (MCP)–polyvinyl chloride (PVC) membrane sensor are described. The sensor is based on the use of MCP–tetraiodomercurate ion pair as electroactive material in PVC matrix in presence of dioctylphthalate (DOP) as solvent mediator. MCP membrane sensor shows a stable, near Nernstian response over the concentration range 1×10^{-2}–6×10^{-5} M of MCP at 25 °C in the pH range 3–7 with cationic slope of 53.0 ± 0.5. The detection limit of 4×10^{-5} M and the response time of 30–60 s have been attained. Selectivity coefficient data for some common ions show negligible intereferences. Direct potentiometric determination of 15–3540 μg/ml MCP show an average recovery of 98.5% and a mean relative standard deviation (R.S.D.) of 1.6% at 100.0 μg/ml. The determination of MCP in Primperan tablets, injection, and syrup gave results that compare favorably with those obtained by the British pharmacopoeia method. Precipitation titrations involving MCP as titrant are monitored with the MCP sensor for some potentiometric precipitation reaction, e.g. sodium tetraphenylborate (STPB) and phosphomolybdic acid (PMA).

Keywords: MCP; Tetraiodomercurate; PVC membrane sensor; Potentiometric determination

1. Introduction

Metoclopramide [monohydrate of 4-amino-5-chloro-*N*-(2-diethylaminoethyl)-2-methoxybenzamide hydrochloride (MCP)], is the active ingredient of many pharmaceutical preparations concerned with the modification of digestive behavior [1]. The interest in MCP is related to the elective character of its action in various digestive manifestations commonly seen in medical practice, e.g. nausea, vomiting, hiccup, migraines, digestive dyskinesias, and radiological investigation.



Methods available in the literature for quantification of MCP involve spectrophotometry [2–4],

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fluorimetry [5], differential scanning calorimetry (DSC) and X-ray diffraction [6], liquid chromatography (LC) [7], high performance liquid chromatography (HPLC) [8–11], and gas chromatography–mass spectrometry (GC–MS) [12] have been reported. Most of those methods are complicated and need sophisticated instrument.

Ion selective electrodes have found wide applications [13–22] that are simple, economical, and applicable over a wide range of different nature. Ion selective electrode based on the ion pair complex of MCP with sodium tetraphenylborate (STPB) was recommended for determination of MCP in some pharmaceutical preparation [23]. This work describes the construction, electrochemical evaluation and pharmaceutical applications of novel potentiometric sensor for MCP. This sensor incorporates the ion association complexes of MCP cation with iodomercurate as counter anion in a plasticized polyvinyl chloride (PVC) matrix. The MCP–iodomercurate ion association PVC electrode is the more response, and near-Nernstian stable. The sensor has been successfully applied for the determination of MCP in simple and complex matrices.

2. Experiment

2.1. Apparatus

All potentiometric measurements were made at 25 ± 1 °C unless otherwise stated using a Metrohm pH/ion meter (model 692). A Metrohm double junction Ag/AgCl reference electrode (Metrohm 6.0726.100) containing 3 M potassium nitrate in the outer compartment was used in conjunction with the proposed electrode. A combined pH glass electrode (Metrohm 6.0202.100) was used for all pH measurement. Acetate buffer of pH 4.0 was prepared.

2.2. Reagents and materials

All chemicals used were of analytical reagent grade unless otherwise stated and doubly distilled water was used throughout. Pharmaceutical grade MCP powder and MCP dosage forms were supplied by Memphis Co. for Pharm. and Chemical. Ind., Cairo, Egypt. PVC powders high molecular weight, dioctylphthalate (DOP) and tetrahydrofuran (THF) of purity $>99\%$ were obtained from Aldrich Chemical Company. Standard MCP was freshly prepared by dissolving pure MCP hydrochloride in distilled water. The solution was stored in refrigerator in PVC container.

2.3. Sensor preparation

MCP–tetraiodomercurate ion pair was prepared by, 1 g of solid potassium iodide is dissolved in a solution of about 0.1 g mercury(II) nitrate then added to a clear solution of ~ 0.25 g of MCP in water, a spontaneous white precipitate of MCP–iodomercurate ion pair is formed. The precipitate was filtered off through a Whatman filter paper No. 42, washed with distilled water, dried at room temperature for 24 h and ground to a fine powder. A 10 mg portion of the prepared ion association complex was thoroughly mixed in glass petri dish (5 cm diameter) with 350 mg DOP, 190 mg PVC powder and 5 ml THF. The petri dish was covered with filter paper and left to stand overnight to allow slow evaporation of the solvent and formation of the sensing membrane. The PVC master membrane (≈ 0.1 mm thick) was obtained and sectioned with a cork borer (10 mm diameter) and glued to a polyethylene tube (3 cm length, 8 mm i.d.) using THF as previously described [24,25]. A laboratory made electrode body was used, which consisted of a glass tube, to which the polyethylene tube is attached at one end and filled with internal reference solution (1×10^{-2} M aqueous MCP/KCl). Ag/AgCl internal reference electrode (≈ 1.0 mm diameters) was used. The indicator electrode was conditioned by soaking in a 1×10^{-2} M aqueous MCP solution for 1 h and stored in the same solution when not in use.

2.4. Procedure

The MCP–PVC membrane sensor was calibrated by immersion in conjunction with the reference electrode in a solution of 9 ml of acetate buffer of pH 4 in a 50 ml beaker, then 1 ml different concentration of MCP ranged from $1 \times$

10^{-2} to 1×10^{-5} M was added. The potential was recorded after stabilization to ± 0.2 mV with continuous stirring, and the e.m.f. was plotted as a function of log MCP concentration. The resulting calibration graph was used for subsequent determination of unknown MCP concentration.

2.5. Determination of MCP in pharmaceutical preparations

For the determination of MCP in pharmaceutical tablets, ten tablets of Primperan were accurately weighed, ground into a fine powder, and mixed. A portion of the powder corresponding to 10 mg of MCP was dissolved in water, filtered through a Whatman No. 1 filter paper and washed with water. The filtrate and washings were collected in 100 ml measuring calibrated flask and diluted to the mark with water.

The content of ten MCP vials were mixed and a volume equivalent to one vial (10 mg) was transferred into 100 ml calibrated flask and completed to the mark with distilled water. Ten milliliter of MCP syrup solution after complete shaking was transferred into 100 ml measuring flask and completed to the mark with distilled water.

The MCP ion selective electrode in conjunction with the reference electrode was immersed in the test solution. The potential reading was recorded when stable and compared with a calibration prepared from pure MCP solutions under identical conditions.

3. Results and discussion

The ion pair agent (tetraiodomercurate) was recommended as ion pair agent [15]. Upon tested this ion pair agent for the preparation of MCP ion association complex, a sparingly soluble MCP: tetraiodomercurate ion associate complex was instantaneously formed. The elemental analysis showed that the composition is 2:1 MCP:tetraiodomercurate.

3.1. Sensor characteristics

The potentiometric response characteristics of MCP sensor based on the use of MCP–tetraiodomercurate ion pair complex as a novel electroactive material. The sensor incorporating membrane with the composition 34.5 wt.% PVC as a plastic matrix, 63.5 wt.% DOP as solvent mediator and 2 wt.% ion pair were prepared and electrochemically evaluated according to IUPAC recommendations [26]. The response characteristics of MCP electrode based on MCP:tetraiodomercurate ion associate complex is summarized in Table 1. The sensor displays a linear response over the concentration range 1×10^{-2}–6×10^{-5} M of MCP with cationic slope of 53.0 ± 0.5 mV per decade and a detection limit of 4×10^{-5} M ($\sim$ 14.2 μg/ml). The least squares equation obtained from the calibration data is:

$$E\ (\text{mV}) = (53.0 \pm 0.4)\log[\text{MCP}] + (191.0 \pm 0.7)$$

3.2. Effect of pH

The electrode response for different MCP concentrations was tested at different pH values, the pH being adjusted using hydrochloric acid or sodium hydroxide solution. Fig. 1, shows the potential response of the electrode dipped into MCP solution of 1×10^{-3}, and 1×10^{-4}, is plotted against the pH of solution. From the graph obtained it is clear that the slope per concentration decade is constant value (53 ± 1.0

Table 1
Response characteristics of MCP–PVC matrix membrane sensor

Parameter	MCP sensor[a]
Slope (mV per decade)	53 ± 0.4
Intercept (mV)	191.0
Correlation coefficient (r)	0.997
Lower detection limit (M)	4×10^{-5}
Response time for [MCP] changed from 1×10^{-4} to 1×10^{-3} M (s)	30 ± 0.5
Working pH range	3–7

[a] Average of five measurements.

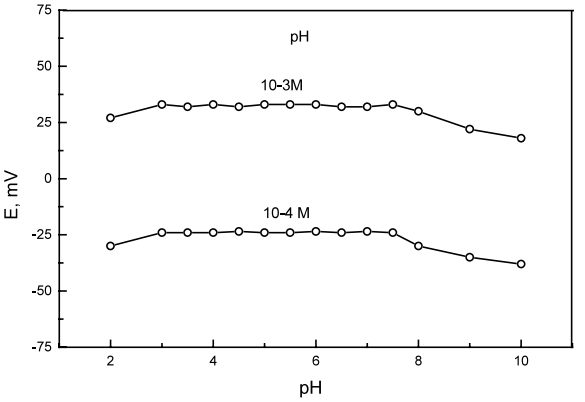

Fig. 1. Effect of pH on the potential response of the MCP–tetraiodomercurate PVC membrane sensor.

mV) and the in the pH range of 3.0–7.0. Below and after pH range (3–7) the potential decreases, while at higher pH value more than 7.5 the MCP is precipitate.

3.3. Response time

The time required for the MCP–iodomercurate electrode to reach steady potential values within ± 1 mV, after successive immersion of the electrode in different concentrations of MCP solutions each having a 10-fold difference in concentration has been measured. The average dynamic response time was found to be short, ranging from 30 s for concentration $\geq 10^{-3}$ M to 60 s for concentration $\leq 10^{-4}$ M.

Day-to-day reproducibility of the sensor is about ±0.5 mV for the same solution and the useful lifetime of the sensor is 4 weeks, during which the potential slope is reproducible to within ±1 mV per concentration decade. Also after more than 6 weeks a new section from the master membrane was found to function very properly.

3.4. Effect of divers ions

The influence of some different organic compound, cation, and anionic on the response of the MCP sensor was investigated. The selectivity coefficients ($K^{pot}_{A,B}$) were determined by the mixed solution method [24,26] in acetate buffer of pH 4.0. The results in Table 2 reveals that there is no intereferences from the studied cations, e.g. K^+, Na^+, Ca^{2+}, Fe^{3+}, Cu^{2+}. Also there is no interference from the investigated anions and some organic compounds except that from cetylpyridinium chloride (CPC).

Table 2
Potentiometric selectivity coefficients of MCP sensor

Interference, B	$K^{pot}_{A,B}$
K^+	2.0×10^{-4}
Na^+	3.7×10^{-3}
Ca^{2+}	2.5×10^{-4}
Fe^{3+}	6.2×10^{-3}
Cu^{2+}	1.3×10^{-2}
CPC[a]	21
L-tryptophan	5.6×10^{-3}
Caffeine	4.9×10^{-3}
Glycine	4.19×10^{-3}
Glucose	5.6×10^{-3}
Fructose	5.6×10^{-3}
Thiourea	6.2×10^{-3}
Tartarate	6.2×10^{-3}
Format	3.2×10^{-3}
CO_3^{2-}	3.7×10^{-3}
SCN^-	8.4×10^{-3}
IO_4^-	2.7×10^{-2}
PO_4^{3-}	1.1×10^{-2}
NO_3^-	9.5×10^{-3}
Cl^-	6.5×10^{-3}

[a] Cetylpyridinium chloride.

3.5. Effect of ionic strength

To study of the effect of ionic strength on the performance characteristics of the electrode aimed to determine the MCP range in which the electrode could be used in different media. The electrode

Table 3
Effect of ionic strength on the performance characteristics of the MCP electrode

Ionic strength	Slope	Analytical range	Lower limit of detection
0.01	53±0.5	1×10^{-2}–6×10^{-5}	4×10^{-5}
0.05	53±0.4	1×10^{-2}–6×10^{-5}	4×10^{-5}
0.1	52±0.5	1×10^{-2}–6×10^{-5}	4×10^{-5}
0.2	52±0.5	1×10^{-2}–6×10^{-5}	4×10^{-5}
0.5	49±0.4	1×10^{-2}–8×10^{-5}	7×10^{-5}
1.0	44±0.4	1×10^{-2}–1×10^{-4}	8×10^{-5}

response (e.m.f.) was measured at different KCl concentration ranging from 0.01 to 0.1 M. From the results (Table 3), it is evident that with increasing the ionic strength to more than 0.2 M KCl causing decrease of the electrode response function (analytical range and lower detection limit). At ionic strength of ≤ 0.2 M KCl, a good response of the electrode with slope of about 53 mV was obtained.

3.6. Analytical applications

3.6.1. Determination of MCP

For verifying the feasibility of the developed method, the determination of MCP in water was carried out. Using the developed membrane electrode the analysis of 15–350 μg/ml MCP solutions (in triplicate) gave an average recovery of 99.0% and relative standard deviation (R.S.D.) (1.7%) at 50.0 μg/ml, results are shown in Table 4.

Although our procedure has to some extent higher detection limit than those described by other techniques of HPLC [8–11] and GC–MS [12], the latters have some limitations (ca. involve several times consuming, often consuming more organic solvent, expensive, and long rune time). Moreover, this procedure is selective, simple, and economical and the higher throughput (about 30 measurements compared with other technique) is distinct advantages of the proposed method. Also, the proposed method is more accurate and precise compared with other reported techniques. The recovery (R, %) and R.S.D. (%) of the proposed method were (97.3–99 and 1.1–1.8%, respectively) compared with other method (R, 94–108% with R.S.D., 1.6–3.6%) [5], (R, 97–106%, and R.S.D., 2.54–9.4%) [8], (R, 92% and R.S.D. $< 6\%$) [7], and (R.S.D., 2.9–12.6%) [12].

Table 4
Potentiometric determination of MCP using MCP–tetraiodomercurate PVC matrix membrane sensor

Added (μg/ml)	Found (μg/ml)	Recovery (%)[a]	R.S.D. (%)
15	14.6	97.3	1.8
25	24.7	98.8	1.6
50	49.5	99.0	1.7
100	98.0	98.0	1.5
150	147.7	98.5	1.3
200	198.0	99.0	1.4
250	246.3	98.5	1.2
350	345.8	98.8	1.2
3540	3504.6	99.0	1.1

[a] Average of three determinations.

The MCP sensor was utilized as an indicator electrode in conjunction with a Ag/AgCl reference electrode for some potentiometric titration. Titration of some anion, e.g. STPB, and phosphomolybdic acid (PMA) with MCP solution has been performed. Fig. 2 shows a typical potentiometric titration curve of tetraphenylborate with MCP. One mole of MCP is consumed per 1 mol of tetraphenylborate. Also Fig. 3 shows a typical potentiometric titration of MCP with PMA, three moles of MCP is consumed per 1 mol of PMA. The inflection break at the equivalence point is about 100 mV for the potentiometric titration of MCP with STPB and PMA, respectively.

MCP was also determined in some pharmaceutical preparations, tables, injection, and syrup. The results obtained (Table 5) show an average recovery of 98.5% of the nominal values and a mean R.S.D. of 1.5% for three replicates which is in agreement with those obtained from the British Pharmacopoeia method (100.6 and 1.8%) [27]. The reliability of the proposed method was statistically examined for the analysis of MCP in some pharmaceuticals preparations in comparison with the British Pharmacopoeia method as shown in Table 5. Comparison between the experimental

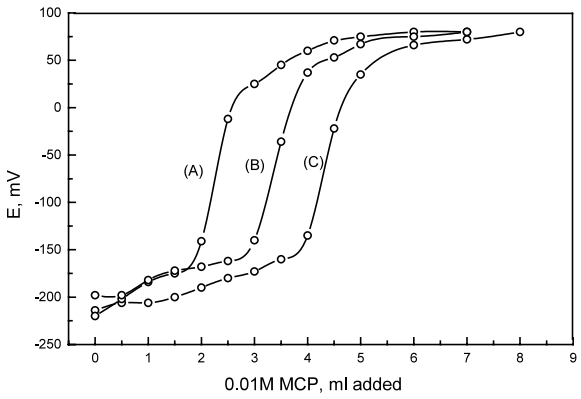

Fig. 2. Typical potentiometric titration curves for (A) 2.5, (B) 3.5, and (C) 4.5 ml of 0.01 M of STPB with 0.01 M MCP using MCP–tetraiodomercurate PVC matrix membrane sensor.

Table 5
Determination of MCP in some pharmaceutical preparations using MCP–PVC membrane sensor

Preparation	Labeled MCP	MCP sensor			British pharmacopoeia			$\|t\|_2$	F
		R (%)[a]	S_1	R.S.D. (%)	R (%)	S_2	R.S.D. (%)		
Primperan (tablet)	10 mg per tablet	98.5	1.47	1.5	98.5	1.67	1.7	0.00	1.04
Primperan (syrup)	0.1 g per 100 ml	98.0	1.66	1.7	101.3	1.72	1.7	3.08	1.07
Primperan (injection)	10 mg per ampoule	99.0	1.38	1.4	102.0	2.04	2.0	2.72	2.18

[a] Average of thee replicates.

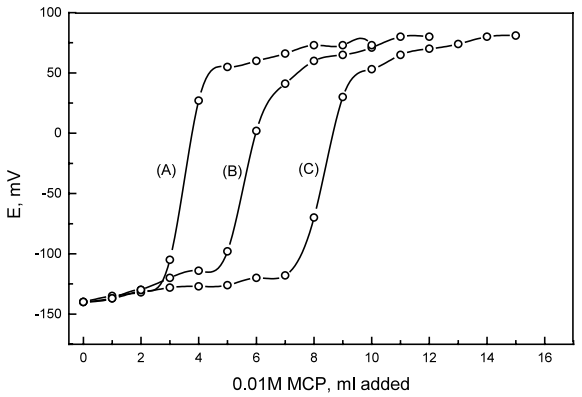

Fig. 3. Typical potentiometric titration curves for (A) 1.0, (B) 2.0, and (C) 3.0 ml of 0.01 M of PMA with 0.01 M MCP using MCP–tetraiodomercurate PVC matrix membrane sensor.

means for the two method was carried out using the null hypothesis of $|t|_2$ for $P = 0.05$ and $n = 3$. It was found that $|t|_2 = 0.0–3.08$, which is less than the tabulated value ($|t|_2 = 3.18$) [28]. No significant difference was found between the two methods, which indicates that the proposed method is accurate as the British Pharmacopoeia method. Comparison between the precession of the proposed method with the British Pharmacopoeia method to estimate the random errors of the two sets of data (Table 5) was also carried out using the two-tailed F-test [28]. From this table it is clear that all the experimental $F_{2,2}$ values are between 1.04 and 2.18. These values are obviously less than the tabulated value of $F_{2,2}$ for $P = 0.05$ and $n = 3$ (39.17) [28]. This proves that the results obtained by the two methods are not subject to random errors. No interference was caused by active or inactive ingredients and diluents commonly used in drug formulations. The sensor, however, offers several advantages in the term of simplicity, selectivity and precision. The proposed method, therefore, can be considered to be suitable for the quality control and routine analysis of the investigated drug in bulk as well as in their dosage forms.

4. Conclusion

It can be concluded that MCP–tetraiodomercurate PVC membrane sensor offers a viable technique for the direct determination of MCP in some pharmaceutical preparations. The sensor is simple, rapid, reproducible and exhibits a good selectivity towards the drug in the presence of various pharmaceutical excipients. The sensor can be used as indicator electrode in some potentiometric titrations.

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