Journal of Advanced Electrochemistry 2(1) (2016) 42–44

ISSN: 2455-0205

Contents List available at JACS Directory

Journal of Advanced Electrochemistry

journal homepage: http://www.jacsdirectory.com/jaec

Determination of Promethazine in Various Pharmaceutical Samples using Promethazine Selective Poly(Vinyl Chloride) Membrane Electrode

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ARTICLE DETAILS

Article history:
Received 26 December 2015
Accepted 05 January 2016
Available online 24 January 2016

Keywords:
Promethazine
Ion-Selective Electrode
Ion-Pair Compound

ABSTRACT

A promethazine hydrochloride and ammonium phosphomolibdtae ion-pair compound was used as electroactive material for selective determination of promethazine in various samples. The electrode of the composition of PVC: PM-PMD: DBP of 33: 3: 64 (%, w/w) has a detection limit of 1.0 x 10^{-6} M in a liner concentration range of 1.0 x 10^{-6} – 1.0 x 10^{-1} M with a slope of 50.5 ± 0.3 (mV/decay of activity). The electrode can be used in a pH range of 2.5 – 6.0 for a period of 4 weeks and has fast response time of about 5 s.

1. Introduction

Promethazine (Fig. 1) is an antihistamine drug, which is used to treat allergy symptoms such as itching, runny nose, sneezing, itchy or watery eyes, hives, and itchy skin rashes. It is a first generation H_1-receptor antagonist. The excessive use of drug may cause serious side effects such as loss of coordination; sever drowsiness, fainting, dilated pupils, weak breathing etc. Thus the determination of drug is subject of great scientific importance especially in pharmaceutical samples [1, 2]. Various methods such as liquid chromatography (HPCL) [3], UV-spectrophotometry [4], capillary electrophoresis [5] voltammetric method [6] have been used for the determination of drug. But all these methods are very expensive and required large infrastructure back up.

The ion-selective electrodes based on ion-pair compound as electroactive material are the good candidature for such determination since they measure activity of target species instead of concentration [7-9]. Several ion-selective poly(vinyl chloride) based electrode were used for the selective determination of various antihistamine drugs [10, 11]. In the present study a highly lipophilic ion-pair compound of promethazine hydrochloride and ammonium phosphomolibdate has been used as electroactive material for the construction of promethazine selective electrode. The selectivity coefficient calculated by match potential method (MPM) indicates that the electrode can be sued for the determination of drug in presence of tested interfering ions.

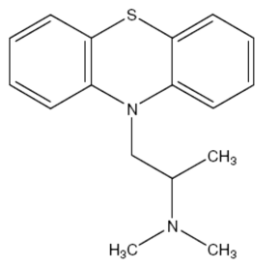

Fig. 1 Structure of Promethazine

2. Experimental Methods

2.1 Reagents and Equipment

The reagents ammonium phosphomolybdate, high molecular weight poly(vinyl chloride), dibutyl phthalate (DBP), dibutylbutyl phthalate (DBBP), oleic acid (OA), 1-chloronaphthalene (CN), tetrahydrofuran (THF) were purchased from Sigma-Aldrich (India). The metal chloride and nitrate salts were purchased from Merck (India). Promethazine hydrochloride and syrup were purchased from local pharmaceutical companies.

2.2 Preparation of Ion-Pair Compound

The ion pair compound of promethazine (Fig. 1) and ammonium phosphomolibdate was prepared by adding 20 mL 0.01M solution of promethazine hydrochloride to 20 mL 0.01 M ammonium phospho molibdate solution. The solution was kept at room temperature for 1 hour under stirring condition. A yellow precipitate of promethazinium phosphomolybdate (PM-PMD) was obtained. The resulting precipitate was filtered off, washed with water and dried over $MgSO_4$ [10].

2.3 Construction of Electrode

The membrane of ion-pair compound was prepared by method available in the literature. The appropriate amount of membrane components *i.e.* PM-PMD, plasticizers (DBP, DBBP, OA and CN) and PVC were dissolved in 25 mL THF and the solution was mixed well to get a homogenous solution. The resulting solution was transferred into a glass dish of 2 cm diameter. The solvent was allowed to evaporate until a concentrated mixture was obtained. A glass tube was dipped into the concentrated mixture for about 10 seconds so a transparent membrane of about 0.3 mm thickness was formed. The glass tube was then pulled out and kept at room temperature for about 5 hr. The membrane was glued properly at one end of glass tube with the help of araldite to avoid the leakage. The tube was filled with an internal solution of 0.001 M Promethazine hydrochloride solution [11-13].

The below cell assembly were used for potential measurements:

Ag / AgCl, 0.1M KCl	Internal reference solution (0.001 M)	PVC Membrane	Test solution	1 M KCl, Ag/AgCl

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Cite this Article as: G. Singh, S. Rani, Determination of promethazine in various pharmaceutical samples using promethazine selective poly(vinyl chloride) membrane electrode, J. Adv. Electrochem. 2(1) (2016) 42–44.

3. Results and Discussion

The response of membrane electrode is highly depends on membrane components and composition. Therefore membranes of various compositions were prepared and their response characters were investigated. The data presented in Table 1 clearly indicates that the membrane based on ion-pair compound promethazinium phosphomolybdate (PM-PMD) as electroactive material has fast response, wide concentration range and low detection limit. Out of all tested membranes the membrane of the composition of PVC: Plasticizer: PM-PMD of 33%: 64%: 3% (w/w) respectively gives the best possible response.

Plasticizer as the membrane component plays a significant role in the response mechanism of membrane electrode. In the present study membranes of various plasticizers were prepared and their response characters were investigated. The membrane electrode (no. 1) based on DBP as plasticizer has a detection limit of 1.0 x 10^{-6} M in a linear working concentration range of 1.0 x 10^{-6} M – 1.0 X 10^{-1} with slope of 50.5 ± 0.3 (mV/dec. of activity). It was observed that 62 – 65% of the plastcizer as membrane components gives the best posible response.

Table 1 Optimization of membrane composition

Electrode No.	Membrane Composition (%)			Linear working range (M)[a] - 1 x 10^{-1}	Slope (mV/dec. of activity)[a]	Response Time (sec)	Life time (weeks)
	PVC	Plasticizer	PM-PMD				
1	33.0	64, DBP	3.0	1.0 x 10^{-6}	50.5 ± 0.3	5	4
2	33.0	64, DBBP	3.0	4.6 x 10^{-5}	46.8 ± 0.3	12	2
3	33.0	64.0, OA	3.0	7.3 x 10^{-5}	46.4 ± 0.3	11	2
4	32.0	64.0, CN	3.0	5.0 x 10^{-5}	45.8 ± 0.3	15	2
5	34.0	62.0, DBP	4.0	8.0 x 10^{-6}	50.4 ± 0.3	5	4
6	33.0	62.0, DBP	5.0	1.2 x 10^{-6}	50.5 ± 0.3	6	4
7	32.0	65.0, DBP	3.0	1.6 x 10^{-6}	50.3 ± 0.3	6	4

The effect of amount of ion-pair compound on the potential response of the electrode was also investigated. It was observed that the ionophore more than 3% (w/w) as membrane component does not improved the detection limit and linear concentration range. Thus 3% of ion-pair compound is sufficient for the smooth functioning of the electrode assembly. The variation of potential with concentration for different plasticizer is shown in Fig. 2.

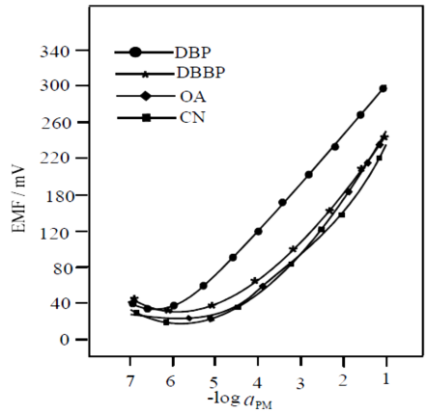

Fig. 2 Effect of concentration on potential response of different electrodes

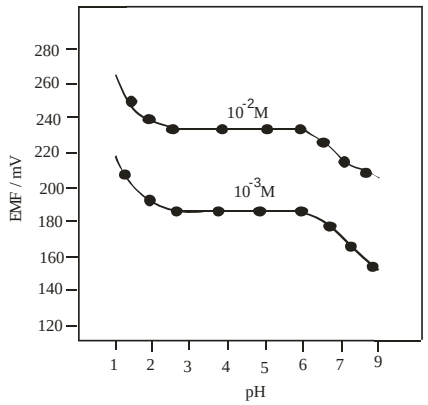

Fig. 3 Effect of pH on response character of electrode no. 1

3.1 pH Effect

The effect of pH on potential response for electrode no. 1 was investigated in the range of 1.0 – 9.0. It was observed that the potential of electrode assembly remains almost same in a pH range of 2.5 to 6.0. Thus the proposed membrane electrode no. 1 can be used for the selective determination of promethazine within a pH range of 2.5 – 6.0. However a significant variation on potential response was observed at pH < 2.5 and at pH> 6.0. This is probably due to the interference caused by H^+ and OH^- ion in acidic and basic medium respectively. The pH of test solution was adjusted by adding standard HCl and NaOH solution (Fig. 3).

3.2 Response Time and Life Time

The time required to generate a static potential is called static response time. In the present study the response time of electrode no. 1 was calculated by changing the concentration of test solution from 1.0 x 10^{-6} M to 1.0 x 10^{-1} M. it was observed the electrode gets the equilibrium value of potential in a very short time of about 5 seconds. The variation of potential with time for 0.01 M and 0.001 M solution of promethazine is shown in Fig. 4. It is very important to mention here that the response time for higher concentration is slightly more than 5 s. The average response time for whole concentration was 5 s.

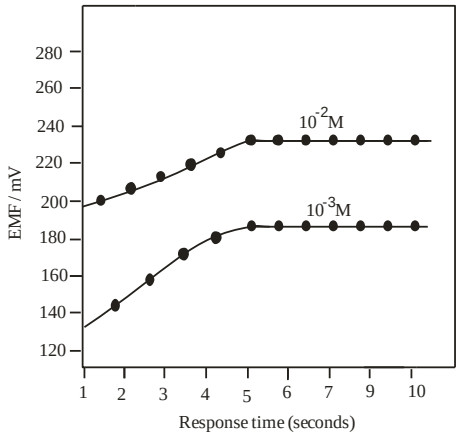

Fig. 4 Response time curve for electrode no. 1

The life time of membrane electrode was calculated in terms of detection limit and slope of calibration curve. It was observed that the detection limit and slope remains almost same (up to 95%) for a period of 4 weeks. After this period the detection limit and slope decreases significantly because of leaching of membrane components into the solution (Table 2).

Table 2 Change in detection limit and slope with time for electrode no. 1

Time (weeks)	Detection limit (M)	Slope (mV/dec.)
1	1.0 x 10^{-6}	50.5 ± 0.3
2	1.0 x 10^{-6}	50.0 ± 0.3
3	1.2 x 10^{-6}	59.2 ± 0.3
4	2.0 x 10^{-6}	48.1 ± 0.3
5	9.0 x 10^{-6}	40.5 ± 0.3
6	1.5 x 10^{-5}	28.6 ± 0.3

3.3 Selectivity Coefficient

The analytical applicability of membrane electrode is highly dependent on selectivity and sensitivity of electrode towards a target species. It indicates the selective response of the electrode towards a target species in presence of other interfering ions. In the present study the selectivity of promethazine electrode was investigated in terms of potentiometric selectivity coefficient calculated by matched potential method (MPM) [14]. According to this method, a specified activity of the primary ion (A) is added to a reference solution and the potential is measured. In a separate experiment, an interfering species (B) is successively added to an identical reference solution (containing the primary ion), until the measured potential matches the one obtained with the primary ions. The matched potential method selectivity coefficient, K^{MPM}, is then given by the resulting primary ion to the interfering ion activity (concentration) ratio, $K^{MPM} = a_A/a_B$ [15, 16]. The selectivity coefficients of membrane electrode no. 1 were also compared with the previously reported promethazine selective electrode [17, 18]. The resulting values of the selectivity coefficients are shown in terms of in Table 3. As seen from the data in Table 3 the reported electrode is superior with the previously reported electrode.

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Table 3 Selectivity coefficients of various interfering ions (B)

Interfering species B	Selectivity coefficient (-log $K_{PM,B}^{MPM}$)	
	This work	[17]
Li^+	3.96	-
Na^+	4.32	3.93
K^+	4.99	4.88
NH_4^+	4.67	4.33
Mg^{2+}	4.80	4.82
Ca^{2+}	4.89	4.90
Zn^{2+}	4.67	-
Fe^{3+}	4.90	-
Cl^-	4.25	-
NO_3^-	4.72	-
Glucose	3.80	3.21
Lactose	3.89	-

The response characters of the electrode no. 1 were also compared with previously reported electrode. The compression data are shown in Table 4. This Table also indicates the superiority of electrode no. 1 over previously reported electrode.

Table 4 Comparison study of reported electrode with previously reported electrode

Reference	Working concentration range (M) ^{6} – 1.0×10^{-1}	Detection limit (M)	Slope (mV/decay)	Response time (s)	pH range
This work	1.0×10^{-5}	1.0×10^{-6}	50.5 ± 0.3	5	2.5 – 6.0
[17]	1.0×10^{-5}	1.0×10^{-5}	54.5 ± 0.3	5	3.5 – 6.3
[18]	5.0×10^{-5}	2.0×10^{-5}	-	<20	-

3.4 Analytical Applications

The proposed electrode no. 1 was successfully applied to determine promethazine concentration in various pharmaceutical samples. The concentration of drug was determined by using calibration method and the results are summarized in Table 5. The data presented in Table 5 indicates the recoveries of drug by electrode no. 1 are in good agreement with the labeled concentration. The test solutions of drug were prepared by adding a definite amount of drug syrup (2 mL) in 10 mL of water in a volumetric metric flask.

Table 5 Recovery of drug from different pharmaceutical samples

Syrup sample (Company)	Labeled amount	Recovery
Promethazine Syrups (P. P. International)	100 mg/ 100mL	101.3%
Arbro Pharmaceutical Limited	100 mg/ 100mL	100.6%
Pemlis (Grampus Laboratories)	5 mg/60 mL	102.0%
Promethazine 2.5 mg (Euphoria Healthcare Private Limited)	2.5 mg/5 mL	101.0%
Avigan Plus (Monark Biocare Private Limited)	5 mg/ 60 mL	101.2%

4. Conclusion

A promethazine phosphomolibdate (PM-PMD) ion-pair compound was used as electroactive material for construction of promethazine selective electrode. The electrode of the composition of PVC: PM-PMD: DBP of 33: 3: 64 (%, w/w) has a detection limit of 1.0×10^{-6} M in a liner concentration range of 1.0×10^{-6} – 1.0×10^{-1} M with a slope of calibration curve of 50.5 ± 0.3 (mV/decay of activity). The electrode can be used in a pH range of 2.5 – 6.0 for a period of 4 weeks and has fast response time of about 5 s. The selectivity coefficient calculated by MPM method indicates that the electrode can be alllied for the determination of promethazzine in presense of other interfering ions.

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