Plasma-Polymerized Membrane Electrode for the Determination of Dextromethorphan and Dimemorfan

Norio HAZEMOTO,*[,a] Shingo ISHIZAKA,[a] Makoto HAGA,[a] Yuriko KATO,[a] Shigeru KUROSAWA,[b] Naoki KAMO[b] and Yonosuke KOBATAKE[b]

Faculty of Pharmaceutical Sciences, Science University of Tokyo,[a] Ichigaya-funagawara-machi, Shinjuku-ku, Tokyo 162, Japan and Faculty of Pharmaceutical Sciences, Hokkaido University,[b] Kita-12, Nishi-6, Kita-ku, Sapporo 060, Japan. *Received December 23, 1988*

Ion-selective electrodes (ISEs) responsive to the antitussives dextromethorphan and dimemorfan were constructed by the fixation of an ion-exchanger, ammonium tetraphenylborate, on a Millipore membrane by means of a plasma-polymerization technique. The electrodes showed a Nernstian response over the range of 10^{-5}—10^{-2} M dextromethorphan and dimemorphan, and the working pH range was 5—7. The interference from common cations such as Na^+, K^+ and Ca^{2+} was negligible but some organic cations interfered weakly. The electrodes were applied successfully for the determination of the drugs in pharmaceutical preparations.

Keywords plasma-polymerized membrane; ion-selective electrode; dextromethorphan; dimemorphan; potentiometric determination

Potentiometric methods are simple and rapid for pharmaceutical analysis when a suitable sensor is available, and many ion-selective electrodes have been successfully developed for the determination of various drugs such as ephedrine,[1] sulfa drug,[2] quinine,[3] cimetidine and ranitidine.[4] Most of the electrodes reported are of the liquid membrane or polymer membrane type. The liquid membrane type is prepared by dissolving an ion-exchanger in organic solvent,[5] and the latter type is constructed by immobilizing wet membrane components containing the ion-exchanger within polymer membrane matrixes.[6] In both types of electrodes, however, there is a possibility of leakage of an ion-exchanger from the membrane phase, resulting in poor performance of the electrode as regards the detection limit[7] and life time.[8] Therefore, it would be worthwhile to attempt the fixation of ion-exchangers to the polymer matrix membrane.[9]

In a recent publication, some of the authors have reported on a new type of membrane electode[10] whose ion-exchangers were polymerized on a membrane filter by the plasma-polymerization technique. The polymerized membrane is strongly bound to the support and highly resistant to chemical and physical treatments.

In this paper, the construction of a plasma-polymerized membrane electrode responsive to dextromethorphan and dimemorfan is described. The electrodes exhibited satisfactory sensitivity and selectivity for the determination of the drugs either in pure form or in pharmaceticals.

Experimental

Materials Sodium tetraphenylborate (NaTPB) was purchased from Dojindo Laboratories. Di-*n*-octyl phthalate (DOP) was obtained from Nacalai Tesque and dextromethorphan hydrobromide was from Wako Pure Chemical. Dimemorfan phosphate was a generous gift from Yamanouchi Pharmaceutical Co., Ltd. All chemicals used were of analytical reagent grade.

Membrane Preparation The apparatus and procedure for plasma-polymerization have been described previously.[10] Briefly, NH_4TPB monomer was prepared by filtration of the precipitate formed from equimolar solutions of NH_4Cl and NaTPB. The monomer was vaporized at 60—75 °C under an atmosphere of pure Ar of 10 Pa. The distance between the parallel-plate electrodes was 3.5 cm and the power of glow-discharge was 100 W at 13.56 MHz. The membrane for ISEs was prepared with the use of a Millipore filter (VSWP 02500, 0.025 μm nominal pore size, Bedford, Massachusetts) which served as the support for the plasma-polymerization. The plasma-polymerization was performed with a duration of discharge of 6 s, followed by soaking in DOP. After overnight soaking, the membrane was taken out and wiped with filter paper.

Potential Measurements The electromotive force (e.m.f.) across the plasma-polymerized membrane was measured by using the following cell: Ag; AgCl, KCl (saturated) | KCl (saturated) | reference solution || plasma-polymerized membrane || sample solution | KCl (saturated) | KCl (saturated), AgCl; Ag. An aqueous solution containing 10^{-2} M of drugs was used as the reference solution. All measurements of e.m.f. were made at 25 ± 1 °C using an electrometer connected to a pen recorder. The sample and reference solutions were stirred throughout measurement.

Potentiometric Assay of Pharmaceutical Preparations An appropriate amount of dextromethrophan powder was dissolved in a 0.01 M H_2SO_4 solution by stirring for 1 h. The solution was diluted with water so as to obtain a final concentration in the range of 10^{-3}—10^{-4} M and the pH was adjusted to 6 by adding a small volume of NaOH solution. At least five tablets of dimemorfan were powdered and a portion of the powder was dissolved in diluted sulfonic acid as described above. The concentration of the background electrolyte in the sample solutions was limited to about 10^{-2} M to minimize the effect of ionic strength. An aliquot (8 ml) of the resulting solutions was analyzed by the standard addition method and the calibration graph method.

Results and Discussion

Membrane potentials across the plasma-polymerized membrane are plotted against the logarithm of concentration of dextromethorphan and dimemorfan in Fig. 1. The electrode exhibited a linear response with the slope of 59.1 mV/decade or 58.4 mV/decade at 25 °C over the range

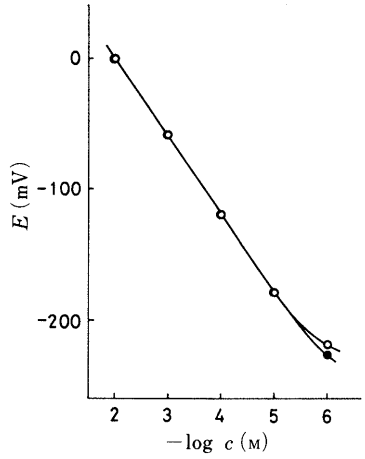

Fig. 1. Response Curve of the Plasma-Polymerized Membrane Electrode

○, dextromethorphan electrode; ●, dimemorfan electrode. The concentration of the reference solution was 10^{-2} M.

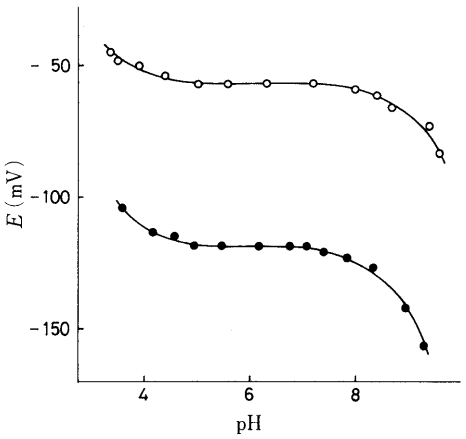

Fig. 2. Effect of pH on the Potential of the Dextromethorphan Electrode

The concentrations of the sample solution were: ○, 10^{-3}; ●, 10^{-4} M.

of 10^{-2}—10^{-5} M dextromethrophan or dimemorfan, respectively. Dimemorfan gave slightly greater sensitivity than dextromethorphan. The membrane potential reached a steady value within 5—10 s and was stable for several hours in the concentration range of 10^{-2}—10^{-5} M. Below this level the response times were longer, but did not exceed 1 min in either case. The life time of these electrodes was at least 6 months, as reported previously for a plasma-polymerized membrane electrode.[10] It was necessary, however, to store the membrane in DOP when it was not in use.

Effect of pH The effect of pH on the potential of the dextromethorphan electrode was examined by measuring the e.m.f. of the cell at 10^{-3} and 10^{-4} M dextromethorphan concentrations. The pH was varied by adding appropriate amounts of sulfonic acid and/or sodium hydroxide solution. As shown in Fig. 2, the electrode potentials were not affected by pH in the range of 5—7. The significant increase of the potential observed below pH 5 may be due to interference by H^+, and the decrease of the potential above pH 7 is probably due to the increase of noncharged species arising from deprotonation, or the precipitation of the free base.

Selectivity of the Electrode The selectivity coefficients, K_i, were evaluated according to the following equation,

$$\Delta\Psi = \Delta\Psi_O + (RT/F)\ln(C_d + K_i C_i)$$

where C_d and C_i denote the concentrations of dextromethorphan and an interfering substance, respectively. $\Delta\Psi$ is a potential change observed and $\Delta\Psi_O$ is a constant. The potential change was measured in mixed solutions that contained either 10^{-3} or 10^{-4} M dextromethorphan solution and 10^{-2}—10^{-5} M of the interfering substance. Selectivity coefficients obtained are presented in Table I. Negligible interference was found in the presence of common inorganic cations and amino acids. Weak interference was observed with some of the organic cations such as tetraethylammonium and atropine. Dimemorfan interferes seriously, which is to be expected, as dextromethorphan and dimemorfan have similar structures.

Assay of Dextromethorphan and Dimemorfan in Pharmaceutical Preparations The drugs present in pharmaceutical preparations can be determined by the standard addition method after their dissolution in acidic solution.

Table I. Selectivity Coefficients for Dextromethorphan Electrode

Interfering species	Selectivity coefficient	Interfering species	Selectivity coefficient
NaCl	$<2.0\times10^{-4}$	Glycine	$<4.0\times10^{-4}$
KCl	3.8×10^{-4}	Histidine	$<4.0\times10^{-4}$
NH_4Cl	1.9×10^{-3}	Lysine	$<4.0\times10^{-4}$
$CaCl_2$	$<2.0\times10^{-4}$	Creatinine	1.8×10^{-3}
Glucose	$<2.0\times10^{-4}$	Acetylcholine	$<4.0\times10^{-4}$
Urea	$<2.0\times10^{-4}$	Atropine	7.5×10^{-3}
$(C_2H_5)_4NCl$	2.3×10^{-3}	Dimemorfan	1.7

Table II. Determination of Dextromethorphan and Dimemorfan in Pharmaceutical Preparations by the Standard Addition Method

Compound	Content (mg/g or mg/tablet)			
	Nominal	Found	Recovery	C.V. (%)
Medicon (Dextromethorphan powder)	100	102	102	3.3
Astomin (Dimemorfan tablet)	10	10	101	3.6

The concentration (C_1) of the sample extracted from the commercial products was calculated from

$$C_1 = C_2V_2/(10^{\Delta\Psi/S}(V_1+V_2)-V_1)$$

where V_2 and C_2 denote the volume and the concentration of added standard drug solution, respectivey, $\Delta\psi$ is the potential change, S is the slope of the elctrode response, and V_1 is the volume of the initial sample solution.

The results of the assay for dextromethorphan in powder and dimemorfan in tablets are presented in Table II. In both instances, the recovery was good and the coefficient of variation was less than 4%. The determination of 1—1000 μg/ml dimemorfan in extracted solution was also done by the calibration graph method. The results obtained showed an average recovery of 101.6% of the nominal values, and the mean standard deviation was 3.2%. Thus, the new electrodes may provide a rapid and inexpensive method for the determination of dextromethorphan and dimemorfan in pharmaceutical preparations.

Acknowledgement The authors are grateful to Prof. I. Horikoshi, Department of Hospital Pharmacy, Toyama Medical and Pharmaceutical University, for providing dextromethorphan, dimemorfan and their commercial preparations.

References

1) K. Fukamachi, R. Nakagawa, M. Morimoto and N. Ishibashi, *Bunseki Kagaku*, **24**, 428 (1975).
2) N. Hazemoto, N. Kamo and Y. Kobatake, *J. Pharm. Sci.*, **65**, 435 (1976).
3) J. Anzai, C. Isomura and T. Osa, *Chem. Pharm. Bull.*, **33**, 236 (1985).
4) A. M. Papazoglou, E. P. Diamandis and T. P. Hadjiioannou, *J. Pharm. Sci.*, **76**, 485 (1987).
5) H. Freiser (ed.), "Ion-selective Electrodes in Analytical Chemistry," Plenum Press, New York, 1978.
6) G. J. Moody and J. D. R. Thomas, "Ion Selective Electrodes," Merrow Watford, 1971.
7) N. Ishibashi, H. Kohara and N. Murakami, *Bunseki Kagaku*, **21**, 1072 (1972); N. Kamo, N. Hazemoto and Y. Kobatake, *Talanta*, **24**, 111 (1977); N. Kamo, Y. Kobatake and K. Thuda, *ibid.*, **27**, 205 (1980).
8) U. Uesch and W. Simon, *Anal. Chem.*, **52**, 692 (1980).
9) P. C. Hobby, G. J. Moody and J. D. R. Thomas, *Analyst*, **108**, 581 (1983); A. Jyo, T. Imato, K. Fukamachi and N. Ishibashi, *Chem. Lett.*, **1977**, 815 (1977); O. Tahara and T. Oka, *Bunseki Kagaku*, **31**, 397 (1982).
10) S. Kurosawa, N. Kamo, Y. Kobatake and I. Toyoshima, *J. Membr. Sci.*, in press.