A Widely Applicable Electrode Sensitive to Basic Drugs Based on Poly(vinyl chloride) Membrane Plasticized with Tricresyl Phosphate

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A plastic membrane ion-selective electrode applicable to many basic drugs has been developed. The electrode developed was constructed with tricresyl phosphate and a poly(vinyl chloride) matrix on a polytetrafluoroethylene film. The electrode showed a near-Nernstian response to chlorpromazine, trihexyphenidyl, imipramine, dibucaine, papaverine, propranolol, tetracaine, trazodone, quinidine and cinnarizine. The determination of 50 to 3000 μg/ml of trazodone hydrochloride in a pH 4.0 acetate buffer solution showed an average recovery of 99.4% (mean standard deviation 0.7%) by direct potentiometry. Inorganic cations and pharmaceutical excipients did not interfere with the determination. Trazodone hydrochloride and trihexyphenidyl hydrochloride in tablets were determined, and the results compared favorably with those obtained by conventional methods.

Keywords ion-selective electrode; basic drugs; pharmaceutical analysis; poly(vinyl chloride) membrane electrode; tricresyl phosphate; potentiometry

Over the last several years, many ion-selective electrodes have been developed for the determination of ionic drugs because of their advantages of simplicity, rapidity and economy.[1,2] Most of these electrodes were constructed with a membrane containing an ion-exchanger formed from a drug and a lipophilic ion-pairing agent.[2] Electrodes equipped with a plastic membrane, which are highly sensitive to oleophilic ions,[2–4] have been used only for ion-pair formation-based titrations. The membrane has been finally saturated irreversibly with the ion-pair of a target drug and a titrant, and the electrode turns out only for the target drug. Hence, construction of a different electrode is required for each target drug.

Medical drugs, including ionic drugs, should be determined by simple and rapid analytical methods to assure quality control. Widely applicable ion-selective electrodes are suitable for these methods. The authors noted a possibility of a simple polymer membrane electrode constructed with dioctylphthalate–poly(vinyl chloride) (DOP–PVC), which had been applied to direct potentiometry for an individual target drug.[5] We therefore dealt with simple polymer membrane electrodes and report that some of them have wide applicability to various ionic drugs.

Experimental

Reagents Tricresyl phosphate (TCP), dibutyl sebacate (DBS), dioctyl phthalate (DOP), trioctyl phosphate (TOP) and 1,2-dimethyl-3-nitrobenzene (DNB) were purchased from Wako Pure Chemicals (Osaka, Japan). Triphenyl phosphate (TPP) and dibutyl phthalate (DBP): Tokyo Kasei Kogyo (Tokyo, Japan). Bis(1-butylpentyl) adipate (BPA), dioctyl adipate (DOA), dioctyl sebacate (DOS), trioctyl trimellitate (TOT), bis(1-butylpentyl)decane-1,10-diyl diglutarate (ETH 469) and tetra-*n*-undecyl-3,3′,4,4′-benzophenone tetracarboxylate (ETH 2041): Fluka (Buchs, Switzerland). Trioctyl phosphine oxide (TOPO), dioctylphenyl phosphate (DOPP), *o*-nitrophenyloctyl ether (NPOE), *o*-nitrophenylphenyl ether (NPPE) and 2-fluoro-2′-nitrodiphenyl ether (FNDPE): Dojin Chemicals (Kumamoto, Japan). PVC (high relative molecular weight): Aldrich (Milwaukee, WI, U.S.A.). All of the other chemicals and drugs used were of the best available commercial grade. Reslin tablet® and trihexyphenidyl hydrochloride tablet were obtained from Kanebo, Ltd. (Osaka, Japan).

Electrode Preparation The polymeric membranes were prepared according to the method described previously[6] by using a liquid membrane electrode kit (Denki Kagaku Keiki, Tokyo, Japan). A plasticizer (100 mg) and PVC (40 mg) were dissolved in 1 ml of tetrahydrofuran. A polytetrafluoroethylene (PTFE) membrane filter (Fluoropore®, 0.22 μm, Sumitomo Electric, Japan) was dipped in the mixture and placed on top of the electrode kit. Several drops of the mixture were applied to the PTFE membrane and the membrane was air dried at room temperature. The internal reference solution of the electrode was a 0.1 M LiCl.

Apparatus All potentiometric measurements were carried out by a model EA 920 expandable ion analyzer (Orion Research, Cambridge, MA, U.S.A.) equipped with a strip-chart recorder. The electrodes constructed were used with an Orion Ag–AgCl double-junction reference electrode (Model 90-02) containing 10% potassium nitrate in the outer compartment. The pH and temperature measurements were performed with an Orion pH electrode (Model 91-04) and an Orion automatic temperature compensator, respectively.

Electron Motive Force (emf) Measurements Cell assemblies of the following type were used: Ag–AgCl| 0.1 M LiCl solution || membrane || test solution (acetate buffer, pH 4.0, $I=0.1$)| Ag–AgCl double-junction reference electrode. All measurements were made at 25 ± 1 °C with continuous stirring of the solutions by using a magnetic stirrer. The electrode was washed with deionized water after measurements were made.

Selectivity Coefficients The selectivity coefficients of drugs against chlorpromazine were evaluated by the mixed solution method according to IUPAC recommendations.[7] The potential was measured with solutions which had a constant concentration of drug and varying concentrations of chlorpromazine, from 10^{-3} to 10^{-6} M. The selectivity coefficients of alkylammonium ions against trazodone were evaluated by the separate solution method.[7] The potential was measured in 10^{-3} M solutions of the corresponding compounds. The selectivity coefficients of inorganic cations were evaluated by the mixed solution method. The potential was measured with solutions of a constant concentration of interference and varying concentrations of trazodone 10^{-4} to 10^{-5} M.

Influence of Excipients The influence of pharmaceutical excipients was determined from the quantity of the excipients that produced a ±0.3 mV change in emf value to 150 μg/ml of a trazodone hydrochloride solution. This change (0.3 mV) corresponded to an error of 1% trazodone hydrochloride content for the assay of trazodone hydrochloride in tablets by direct potentiometry as described below.

Determination of Drugs in Tablets by Direct Potentiometry Standard Solution: Two standard solutions, I and II, in acetate buffer (pH 4.0) having the known concentrations of drug of 120 and 180 μg/ml, respectively, were prepared.

Assay Solution: Pharmaceutical preparations were finely powdered. An accurately weighed portion of the powder, equivalent to about 15 mg of drug, was added to about 80 ml of acetate buffer (pH 4.0) and sonicated for 5 min, then additional acetate buffer was added to make exactly 100 ml.

Procedure: The plastic membrane ion-selective electrode and the Orion double-junction reference electrode were immersed successively in standard solution I, the assay solution and standard solution II. The respective emf values of these solutions were determined. The quantity was calculated by the calibration line obtained from the two standard solutions.

Determination of Apparent Partition Coefficients The drugs were partitioned between chloroform saturated with acetate buffer (pH=4.0, I=0.1) and acetate buffer saturated with chloroform. Each drug was first dissolved in acetate buffer. Each 4 ml aliquot of drug solution and chloroform was shaken for 30 min at 20 °C. After centrifugation, the concentration of the sample both in the aqueous and organic phase was determined by the HPLC method. Each determination was done in duplicate, and the mean was determined.

Results and Discussion

Selection of Plasticizer The plasticizers tested are shown in Table I together with the response characteristics of the corresponding electrodes. The composition of the membranes was a mixture of 71% (w/w) plasticizer and 29% (w/w) PVC, which was reported to be the most suitable.[8] The response of these electrodes was examined by using trazodone hydrochloride so that the responses of the present electrodes could be evaluated in comparison with the previously developed trazodone-selective electrode.[6] It should be noted that several electrodes tested, including the DOP–PVC electrode,[5] responded to trazodone as seen in Table I. This suggests that some membranes constructed only with plasticizer and PVC have the potential to be widely applicable electrodes to basic drugs. Although many electrodes showed a near-Nernst response, the slopes of the TCP–, TPP–, and DOS–PVC electrodes were closest to the theoretical response (59 mV/log C). Moreover, the TCP–PVC electrode was superior to the TPP– and DOS–PVC electrodes in the stable potential readings and the wide linear–response range, and was comparable with the trazodone-selective electrode consisting of an ion-pair of trazodone and tetrakis(*p*-chlorophenyl)borate.[6] These results indicate that the TCP–PVC electrode is most suitable for quality control in certain respects such as slope, wide linear range and stable potential readings. We therefore selected TCP as the plasticizer for a basic drug-selective electrode.

The potential readings of the TCP–PVC electrode for 10^{-3} M trazodone hydrochloride solution varied by not more than ±0.2 mV over 1 h. The electrode exhibited a day-to-day reproducibility of slope of ±0.7 mV/decade and its intercept was ±8 mV during 4 d. The linear response range was not changed, and the slope was stable within ±1.1 mV/decade over 2 months. These results indicate that the TCP–PVC electrode can be applicable to the determination of trazodone for at least 2 months.

On the other hand, the BPA–, TOP–, and DBS–PVC electrodes, reported to respond to inorganic cations,[9,10] exhibited less response to trazodone than that of the TCP–PVC electrode in slope and linear range. The NPOE– and DBP–PVC electrodes, which had been investigated for their responses to inorganic cations and/or surfactants,[10,11] did not respond to trazodone.

Electrode Response The critical response characteristics of the TCP–PVC electrode to some basic drugs (Fig. 1) are summarized in Table II, along with their selectivity and partition coefficient. The TCP–PVC electrode responded rapidly in the linear range of the calibration solution, usually equilibrating within 1—2 min after exposure to each concentration. The TCP–PVC electrode showed a near-Nernst response to the drugs tested in the concentration range of less than 10^{-2} M except for etilefrine, as seen Table II. This result indicates that the TCP–PVC electrode, an electrode equipped with a simple polymer membrane, can be widely applied to basic drugs.

The selectivity sequence of the TCP–PVC electrode toward alkylammonium ions was measured to examine the influence of hydrophobicity on the selectivity of the TCP–PVC electrode. As shown in Fig. 2, a plot of log K (K; selectivity coefficient) against the carbon atom number of secondary alkylammonium ions gave a straight line (slope=0.53). Thus, hydrophobicity is one of the causes of selectivity of the TCP–PVC electrode, similarly to the trazodone-selective electrode.[6] On the other hand, Higuchi *et al.* reported that plasticizers having shareable electron pairs solvated hydrophobic organic cations.[4] By analogy with this report, the presence of anionic sites in TCP and/or PVC[12] may contribute to the response of the TCP–PVC electrode.

The selectivity of the TCP–PVC electrode to the drugs had a tendency to increase with the log P values of the drug. The lowest selectivity was for etilefrine, which may be attributed to its low hydrophobicity. However, the hydrophobicity factor is inconsistent in that the most hydrophobic, papaverine, and the lower hydrophobic pro-

Table I. Critical Response Characteristics of Plasticized PVC Membrane Electrodes

Plasticizer	Slope (mV/log C)	Correlation coefficient	Intercept (mV)	Linear response range Trazodone (M)
TCP	54.9±0.3[a]	0.9998	212.0± 0.7	10^{-5}—10^{-2}
TPP	54.9±1.5	0.9998	237.6±24.8	10^{-5}—10^{-2}
BPA	53.2±0.6	0.9989	171.4± 2.2	10^{-5}—10^{-2}
DOA	50.3±0.4	0.9963	178.6± 1.4	10^{-5}—10^{-2}
DBS	52.7±1.8	0.9996	214.7±10.7	5×10^{-5}—10^{-2}
DOP	52.4±1.8	0.9994	209.6± 2.3	5×10^{-5}—10^{-2}
TOP	50.5±0.2	0.9978	183.5± 4.3	5×10^{-5}—10^{-2}
ETH469	53.5±0.7	0.9997	186.2± 2.8	5×10^{-5}—10^{-2}
DOS	54.9±0.2	0.9998	199.1± 0.7	5×10^{-5}—10^{-2}
DOPP	50.8±0.1	0.9985	170.7± 1.6	10^{-4}—10^{-2}
FNDPE	48.6±0.2	0.9967	213.9± 1.2	10^{-4}—10^{-2}
Others[b]	No response			

a) Average value and standard deviation of values (n=3). *b*) DNB, NPOE, NPPE, ETH2041, TOP, DBP, TOT.

Table II. Response Characteristics of the TCP–PVC Electrode for Basic Drugs in Acetate Buffer (pH 4.0)

Drug	Slope (mV/log C)	Linear response range (M)	log K	log P[a]
Chlorpromazine HCl	54.3±1.2	10^{-6}—10^{-3}	0	1.9
Trihexyphenidyl HCl	55.5±1.0	10^{-5}—10^{-2}	−0.5	1.3
Imipramine HCl	56.0±1.7	10^{-5}—10^{-2}	−0.4	1.4
Dibucaine HCl	54.2±1.0	10^{-5}—10^{-2}	−0.9	1.3
Papaverine HCl	54.6±1.2	5×10^{-5}—10^{-2}	−1.2	2.9
Propranolol HCl	53.0±0.3	10^{-5}—10^{-2}	−1.3	−1.1
Tetracaine HCl	54.5±0.5	10^{-5}—10^{-2}	−1.4	0.3
Trazodone HCl	54.9±0.3	10^{-5}—10^{-2}	−1.6	2.0
Quinidine	59.4±0.3	5×10^{-4}—10^{-2}	−2.1	−0.1
Cinnarizine[b]	50.8±0.3	10^{-4}—10^{-2}	—[c]	—[c]
Etilefrine HCl	No responce		<−4.0	<−3.0

a) Partition coefficients (chloroform–pH 4.0 acetate buffer). *b*) A response for cinnarizine was examined in 0.1 N HCl solution because of its low solubility in pH 4.0. *c*) Not measured in pH 4.0 buffer solution.

chlorpromazine hydrochloride

trihexyphenidyl hydrochloride

imipramine hydrochloride

dibucaine hydrochloride

papaverine hydrochloride

propranolol hydrochloride

tetracaine hydrochloride

trazodone hydrochloride

quinidine

cinnarizine

etilefrine hydrochloride

Fig. 1. Structures of Drugs

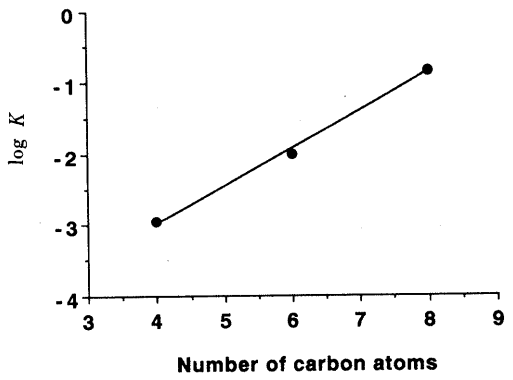

Fig. 2. Plot of log K against the Carbon Atom Number of the Secondary Alkylammonium Ion

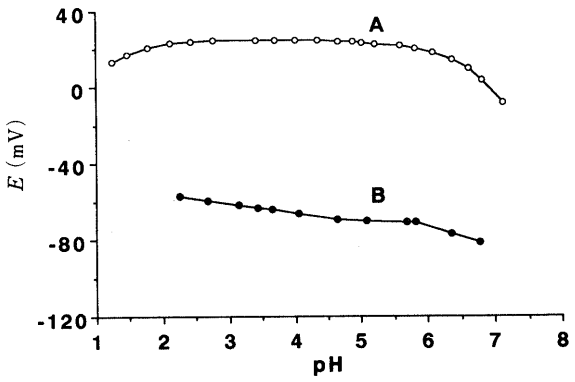

Fig. 3. Effect of pH on the Potential of the TCP–PVC Electrode for (A) 10^{-3} M Trazodone Hydrochloride Solution and (B) 0.1 M LiCl Solution

pranolol both had medium selectivity. This suggests that the selectivity depends not only upon hydrophobicity but also on the strength of the interaction between the anionic sites and the drug, and on the mobilities of the respective ions in the membrane.

Influence of pH The influence of pH on the potential of the TCP–PVC electrode was checked for 0.1 M LiCl solution and 10^{-3} M trazodone hydrochloride solution. As shown in Fig. 3, the TCP–PVC electrode was slightly sensitive to the hydrogen ion in the 0.1 M LiCl solution. However, in the trazodone solutions, the potential was not affected by the hydrogen ion between pH 2.5 and 5.0, similarly to the trazodone-selective electrode. The potential decreases at lower pH values (pH <2.5) because the electrode becomes progressively sensitive to the diprotonated trazodone. [trazodone-$2H^+$] species. At higher pH values (pH >5.0), the potential decreases with the increase in pH because the protonated trazodone, [trazodone-H^+] species gradually decrease.

The potential–pH curve can be used to evaluate the dissociation constants (K_a).[6] The pK_a value obtained from the curve was 6.65, which agreed with the value (6.70) evaluated by the potentiometric titration method.

Influence of Foreign Substances The influence of some

TABLE III. The Allowable Limit of Excipients

Exicipient	Excipient wt.[a]/ Trazodone HCl wt.[b]
Corn starch	>20
Microcrystalline cellulose	>20
Sucrose, lactose, D-mannitol	>20
Synthetic aluminium silicate	>10
Magnesium stearate	> 2
Titanium oxide	> 2
Hydroxypropylcellulose	> 2
Hydroxypropylmethylcellulose 2910	> 2

a) Excipient weight which gives an error of 1%. *b*) Concentration of trazodone HCl is 150 μg/ml.

TABLE IV. Determination of Trazodone HCl in Solution by the TCP–PVC Electrode

Trazodone HCl (μg/ml)		Recovery (%)[a]	Standard deviation
Added	Found		
49.8	48.9	98.2	0.9
99.8	98.2	98.4	0.8
151	149	98.7	0.8
200	195	97.5	1.1
302	307	101.7	1.2
499	494	99.0	0.1
998	1010	101.2	0.4
3013	3022	100.3	0.6

a) Average of three measurements.

TABLE V. Determination of Trazodone HCl and Trihexyphenidyl HCl in Tablets

Sample	Content (mg/tablet)	Electrode method		Reference method	
		Recovery (%)	SD	Recovery (%)	SD
Reslin tablet®[a]	25	98.9 ($n=7$)	0.7	99.5 ($n=3$)	0.1
Trihexyphenidyl HCl tablet	2	99.9 ($n=7$)	0.5	99.3 ($n=7$)	0.5

a) Reslin tablet® contains trazodone HCl.

excipients normally used in pharmaceutical preparations was examined. The quantity of excipient that gives an error of 1% in the potentiometric assay for trazodone in tablet form is shown in Table III. Normal doses of the excipients did not interfere with the determination. Further, inorganic cations, Na^+, K^+, Li^+ and NH_4^+, gave negligible interference ($\log K < -4$ by the mixed solution method). These results indicate that the TCP–PVC electrode is useful for the assay of the drugs in pharmaceutical preparations.

Analytical Applications Reproducibility and accuracy were determined by the direct potential method (see procedure) for trazodone solutions between about 50 and 3000 μg/ml. As seen in Table IV, the results showed an average recovery of 99.4% and a mean standard deviation of 0.7%. The reproducibility of the emf values for different samples was determined from alternate measurements of 10^{-3} M trazodone hydrochloride solution and 10^{-3} M trihexyphenidyl hydrochloride solution. The relative deviations of the emf values ($n=6$) of trazodone and trihexyphenidyl were 0.56 and 0.42%, respectively.

Trazodone hydrochloride and trihexyphenidyl hydrochloride in commercially available tablets was determined by the TCP–PVC electrode method and by the HPLC method[6] for trazodone hydrochloride or by the official method[13] for trihexyphenidyl hydrochloride. The results obtained by both the TCP–PVC electrode and reference methods showed good agreement and high precision (Table V).

In conclusion, the TCP–PVC electrode has the advantage of wide applicability to various basic drugs. This wide applicability may be effective for the detection of the drugs, especially as detector of flow-injection analysis and HPLC. Moreover, because the electrode method without any prior separation offers several advantages in simplicity, most importantly in shortening of time and in economy, the TCP–PVC electrode method can be expected to be substituted for the conventional method in continuous assays of the quality control of pharmaceutical preparations.

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