A Pethidine Selective Polymeric Membrane Electrode Based on Pethidine-Silicotungstate

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Pethidine hydrochloride (Meperidine hydrochloride, Dolantin, Fig. 1) is an important narcotic analgesic.¹ It is also an analogue of illicit drugs, such as heroin. Therefore, it is a controlled substance (opiate) on the list of regulations of many governments. Many methods have been developed for its determination, such as HPLC,^{2,3} GC,^{4,5} GC/MS,^{6,7} colorimetry,⁸ and spectrophotometry,⁹ in which the samples have to be pretreated tediously.

Ion-selective membrane electrodes are widely used for pharmaceutical analysis with advantages of determining sample directly and rapidly.¹⁰⁻¹² In order to determine pethidine hydrochloride in pharmaceutical formulations, Mitsana-Papazoglou *et al.* had developed a liquid membrane pethidine-selective electrode to determine pethidine in injections.¹³ They used *p*-nitrocumene to dissolve ion associate of pethidine with tetrakis(*m*-chlorophenyl)borate. However, *p*-nitrocumene is a carcinogenic compound. It could be leaked during measurements. Therefore, it was not suitable for practical applications. The present authors developed a novel poly(vinyl chloride) (PVC) membrane electrode with dibutyl phthalate as plasticizer based on pethidine-silicotungstate ion-association complex as ion exchange site for determination of pethidine hydrochloride in injections and tablets. The results were correlated well with those obtained by the United States Pharmacopoeia (USP) standard procedure.¹⁴ Compared with Mitsana-Papazoglou's pethidine liquid membrane electrode,¹³ the present plasticized membrane electrode was more stable and had a longer life; in particular, its PVC-based membrane separated the inner solution and the sample effectively. Therefore, it could be useful for on site rapid analysis of pethidine hydrochloride.

Experimental

Reagents

All solutions were prepared with deionized water (resistivity >1 MΩ cm). The chemicals used were all of analytical grade. Silicotungstate was obtained from Aldrich, poly(vinyl chloride) (PVC, high molecular weight) from Fluka, dibutyl phthalate from Sigma, monobasic potassium phosphate, triethylamine and acetonitrile from the local chemical suppliers. The pethidine hydrochloride reference standard was obtained from the

National Anesthetic Drug Laboratory, Beijing, P. R. China. Its characteristics were consistent with those reported by the USP.¹⁴ The standard was treated according to the USP before use.¹⁴ The tablets and injections of pethidine hydrochloride were purchased from a local drug store. Tablets of 25 mg/tablet, 50 mg/tablet, and injection of 50 mg/1 cm³ were manufactured by Qinghai Pharmaceutical Factory, Qinghai, P. R. China. Injection of 100 mg/2 cm³ was produced by Yichang Pharmaceutical Factory of Hubei, Hubei, P. R. China.

Apparatus

Potentiometric measurement was made with a PHs-3C Digital pH-meter (Shanghai Rex Instrument Factory, Shanghai, P. R. China). The external reference electrode was a Model 801 double-junction saturated calomel electrode with outer bridge electrolyte (Jiangsu Electroanalytical Instrument Factory, Jiangsu, P. R. China). A Model E-201-C complex electrode (Shanghai Rex Instrument Factory, Shanghai, P. R. China) was used to measure pH. A XW-80A Vortex (Medicine University of Shanghai, Shanghai, P. R. China) and a CSF-1B ultrasonic generator (Shanghai Ultrasonic Instrument Factory, Shanghai, P. R. China) were used for the dissolution of the tablets. ALC/GPC Model 201 HPLC (Waters, USA) and DL-800 Chromatographic Working Station (Dalian Elite Scientific Instruments Co. Ltd., Liaoning, P. R. China) were employed for determination of tablets and injections of pethidine hydrochloride by USP standard procedures.

Construction of the electrode

The ion-association complex was prepared by mixing stoichiometric amounts of 10⁻² mol dm⁻³ solution of silicotungstate with an equimolar solution of pethidine hydrochloride. The precipitate was filtered and washed with

Fig. 1 The chemical structure of pethidine hydrochloride.

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Fig. 2 The construction of pethidine selective membrane electrode.

Fig. 3 Calibration graph for the pethidine selective membrane electrode at 25°C.

deionized water several times. Then the precipitate was dried under 25°C in vacuum for at least 48 h. The ion-association complex should be stored in a dryer. The preparation of master membrane followed Craggs' procedures.¹⁵ The PVC-membrane composition was 1.0% pethidine-silicotungstate ion-association complex, 66.0% dibutyl phthalate and 33.0% PVC (weight ratio). The electrode body was filled with an inner filling solution containing 10^{-1} mol dm⁻³ NaCl and 10^{-3} mol dm⁻³ pethidine hydrochloride. The construction of the membrane electrode is shown in Fig. 2. The finished electrode was preconditioned overnight by soaking it in a 10^{-3} mol dm⁻³ pethidine hydrochloride solution (saturated with AgCl). The electrode should be washed with deionized water before measurement. It could be kept in air when continuously used. The inner filling solution should be removed when not in use for a long time. All potentiometric measurements were performed using the following cell assembly: Ag/AgCl|KCl(satd.)|| (salt bridge|sample solution|membrane| 10^{-1} mol dm⁻³ NaCl + 10^{-3} mol dm⁻³ pethidine hydrochloride|Ag/AgCl.

Direct potentiometry

Standard solutions of 1×10^{-3} mol dm⁻³ – 1×10^{-8} mol dm⁻³ were prepared by serial dilution of a 1×10^{-2} mol dm⁻³ pethidine chloride solution. The electrodes were placed into well-stirred 10 cm³ standard solutions in the order of 1×10^{-8} mol dm⁻³ – 1×10^{-2} mol dm⁻³ and potentials were recorded. Each calibration

Table 1 Response characteristics of pethidine selective polymeric membrane electrode at 25°C

Parameter	Response
Slope/mV decade ^a	53.77 ± 0.7
Intercept E /mV ^b	270.43 ± 1.2
Linear range/mol dm ⁻³	$1 \times 10^{-5} - 1 \times 10^{-2}$
Detection limit/mol dm ⁻³	9.91×10^{-7}

a. Standard deviation of average slope values for multiple calibration ($n = 50$).

b. Standard deviation of values recorded over a period of 6 months ($n = 50$).

Fig. 4 Effect of pH on the response of the pethidine selective membrane electrode at 25°C (♦: 1×10^{-5} mol dm⁻³; ■: 1×10^{-4} mol dm⁻³; ▲: 1×10^{-3} mol dm⁻³ pethidine hydrochloride solution).

graph was obtained by plotting E (mV) vs. pC. With the mean potential of five measurements the unknown concentration could be derived from the regression equation of the calibration graph.

Standard addition method

An electrode was immersed into a sample of 10 cm³ with unknown concentration (*ca.* 10^{-4} mol dm⁻³) and the equilibrium potential of E_1 was recorded. Then 0.1 cm³ of 1×10^{-2} mol dm⁻³ of pethidine hydrochloride standard was added into the testing solution and the equilibrium potential of E_2 was obtained. From the change of ΔE ($E_2 - E_1$) one can determine the concentration of the testing sample.¹⁶

HPLC measurement

The measurement was carried out when the column was μ Bondapak C18, 3.9×300 mm. Equal volumes (about 20 mm³) of the standard solution and testing sample were injected into the chromatograph separately, and the chromatograms were recorded. Then the responses were measured. From the measurement data, the quantity of pethidine hydrochloride in the sample can be calculated.¹⁴

Results and Discussion

Different ratios of membrane composition were employed to evaluate their effect on the response characteristics of membrane electrode. The results revealed that the best composition of membrane was ion association:PVC:plasticizer

Table 2 Potentiometric selective coefficients for the pethidine selective electrode at 25°C

Interference	K_{IJ}^{Pot}	Interference	K_{IJ}^{Pot}
CaCl ₂	6.10×10^{-3}	Cinchonine	1.35
MgSO ₄	3.32×10^{-3}	Procaine	0.25
K ₂ C ₂ O ₄	4.98×10^{-3}	Caffeine	5.60×10^{-2}
(NH ₄) ₂ SO ₄	5.86×10^{-3}	Acetophenetidine	0.11
NaHSO ₄	0.20	Theobromine	6.85×10^{-2}
Na ₂ CO ₃	2.52×10^{-3}	Theophylline	6.32×10^{-2}
Na ₂ SO ₃	2.50×10^{-3}	8-Hydroxyquinoline	8.06×10^{-2}
Hg(NO ₃) ₂	3.32×10^{-3}	Diazepam	7.14×10^{-2}
KNO ₃	5.37×10^{-2}	DL-Alanine	0.13
H ₂ C ₂ O ₄	7.43×10^{-2}	Cystein	0.67
Na ₂ S ₂ O ₃	3.46×10^{-3}	Benzoic acid	0.15
V _{B6}	7.99×10^{-2}	Berberine	6.38×10^2
V _{B2}	7.03×10^{-2}	Picric acid	0.27
Sodium citrate	1.11×10^{-3}	Fentanyl	4.32
Morphine HCl	7.74×10^{-2}	Thebaine	2.25
Anisodamine	8.06		

= 1%:33%:66% (weight ratio, data not shown). Typical calibration graphs for the pethidine membrane electrode in Fig. 3 showed that electrode response at 25°C was linear in the range of 1×10^{-5} mol dm⁻³ – 1×10^{-2} mol dm⁻³ pethidine hydrochloride solution. The critical characteristics of the electrode are summarized in Table 1. The stability of the electrode response was checked over a period of 6 months. The time required for the electrode to reach 95% of final response was less than 30 s. The electrode response displayed good stability and reproducibility over the test, as shown by the relative standard deviation values in Table 1. The effect of pH on the electrode potential at 25°C was investigated by observing the changes in the potential readings with pH of the solutions (1×10^{-5} mol dm⁻³ – 1×10^{-3} mol dm⁻³ pethidine hydrochloride solution) after addition of small volumes of 3 mol dm⁻³ HCl and/or 3 mol dm⁻³ NaOH. It was found that pethidine-sensitive membrane electrode based on pethidine-silicotungstate ion-association complex showed virtually no pH response over the range of 2 – 8 pH units, as in Fig. 4. In alkaline media, the measurements were hindered owing to the formation of a precipitate in the test solutions. The interferences of various ions and uncharged substances on selectivity of electrodes were studied by the separated solution method (SSM) recommended by IUPAC.¹⁶ The potentiometric selectivity coefficients (K_{IJ}^{Pot}) at 25°C are listed in Table 2. There were no significant interference from most of the tested substances, with the exceptions of berberine, fentanyl, thebaine, cinchoine, picric acid, and procaine. Fortunately, these interferences were absent in pethidine hydrochloride tablets or injections. The proposed electrode was reasonably selective towards pethidine hydrochloride. The proposed electrode was employed for the assay of pethidine content in injection and tablet by standard addition method. The results of the potentiometric methods compared with the USP standard procedure at 25°C are shown in Table 3. As could be seen in Table 3, high precision was obtained (RSD<1%) by the potentiometric method. The pethidine-selective plastic membrane electrode based on pethidine-silicotungstate ion-association complex in a PVC matrix exhibited useful analytical characteristics for the determination of pethidine hydrochloride in pharmaceutical preparations.

Table 3 Comparison of mean values of pharmacopoeia and potentiometric methods for the assay of pethidine hydrochloride in injection and tablet at 25°C

Sample	Potentiometric method		USP standard method ¹⁴	
	Recovery (% of nominal value) ^a	RSD, %	Recovery (% of nominal value) ^a	RSD, %
50 mg/ 1 cm ³ injection	97.20	1.02	91.85	0.77
100 mg/ 2 cm ³ injection	100.42	0.99	93.04	0.75
25 mg/tablet	95.98	0.51	91.32	0.47
50 mg/tablet	97.56	0.73	91.13	0.56

a. All values are the average of 5 determinations.

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References

1. S. White and S. H. Y. Wong, in "Guidelines for Therapeutic Drug Monitoring Services", ed. A. Warner and T. Annesley, **1999**, The National Academy of Clinical Biochemistry, USA, 63.
2. T. G Venkateshwaran, J. T. Stewart, and D. T. King, *J. Liq. Chromatogr. Relat. Technol.*, **1996**, 19, 1329.
3. C. R. Meatherall, D. R. P. Guay, and R. P. Dvid, *J. Liq. Chromatogr.*, **1985**, 338, 141.
4. Y. C. Wong, O. W. Lau, K. Chan, C. Aun, D. M. Lowe, and I. T. Houghton, *J. Biopharm. Sci.*, **1990**, 1, 267.
5. D. E. Coyle and D. D. Denson, *Ther. Drug Monit.*, **1986**, 8, 98.
6. F. Liu, X. Y. Hu, and Y. Luo, *J. Chromatogr., B: Biomed. Appl.*, **1994**, 658, 375.
7. F. Bressolle and J. C. Sleth, *Therapie*, **1988**, 40, 161.
8. R. Giridhar, S. Menou, and Y. K. Agrawal, *Indian J. Pharm. Sci.*, **1987**, 49, 32.
9. H. Farsarn and M. R. Nadjari-Moghaddam, *J. Pharm. Biomed. Anal.*, **1984**, 2, 543.
10. V. V. Cosofret, *Tr. Anal. Chem.*, **1991**, 10, 298.
11. V. V. Cosofret and R. P. Buck, *Crit. Rev. Anal. Chem.*, **1993**, 24, 1.
12. R.-I. Stefan, G.-E. Baiulescu, and H. Y. Aboul-Enein, *Crit. Rev. Anal. Chem.*, **1997**, 27, 307.
13. A. Mitsana-Papazoglou, T. K. Christopoulos, E. P. Diamandis, and T. P. Hadjiioannou, *Analyst*, **1985**, 110, 1091.
14. United States Pharmacopoeia, XXIII ed., **1993**, US Pharmacopoeial Convention Inc., Rockville, 951.
15. A. Craggs, G. L. Moody, and J. D. R. Thomas, *J. Chem. Edu.*, **1974**, 51, 541.
16. R. P. Buck and E. Lindner, *Pure Appl. Chem.*, **1994**, 66, 2527.