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Potentiometric determination of fentanyl in pharmaceutical formulations

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Abstract

A poly (vinyl chloride) membrane electrode with dibutyl phthalate as plasticizer based on the fentanyl-phosphotungstate ion-association complex as ion-exchange site for the determination of fentanyl citrate in injections was developed. A linear response for 1×10^{-5}–1×10^{-2} mol dm^{-3} drug with a slope of 55.9 ± 0.4 mV per decade was established. The optimum pH range was 1–7. The lower detection limit was 5.43×10^{-6} mol dm^{-3} fentanyl citrate (1.827 μg cm^{-3}, 2.33×10^{-6} mol dm^{-3} fentanyl). There were negligible interference from a number of inorganic cations, structural analogues, and some common drug additives in injections. The electrode proposed had been successfully applied to determine fentanyl citrate in injections. The results correlated well with those obtained by the United States Pharmacopoeia standard procedure.

Keywords: Fentanyl citrate; Potentiometric method; Pharmaceutical analysis

1. Introduction

Fentanyl, *N*-(1-phenethyl-4-piperidyl) propionanilide, is a synthetic opiate analgesic, which is 50–100 times more potent than morphine. It acts in the central nervous system to relieve pain and widely used in surgical anesthesia as the citrate salt at doses ranging from 2 to 50 μg kg^{-1}. Meanwhile, fentanyl is also an analogue of illicit drugs, such as heroine, and is highly addictive for abuse. It is significantly more potent than heroine ($\sim 40\times$). It has been sold on the street as heroine causing some death. Illicit use of pharmaceutical fentanyls first appeared mid of 1970s in the medical community and continued to be a problem in the United States. Therefore, various methods have been developed for its quantitative determination, e.g. radioimmunoassay (RIA) [1–5,11,16,28], radioreceptor assay (RRA) [6–8], enzyme-linked immunosorbent assay (ELISA) [9–13], fluoroimmunoassay (FIA) [14], gas chromatography (GC) [15–20], capillary gas chromatography (CGC) [21–23], gas chromatography-mass spectrometry (GC–MS) [4,21,24–28], gas liquid chromatography (GLC) [29], high performance liquid chromatography (HPLC) [30–36,38], micellar electrokinetic capillary chromatography [37],

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thin-layer chromatography [38], and electroencephalography [39] etc. Most of these method were either time-consuming or required expensive or sophisticated instrumentation, however, some of them had excellent detection limits and accuracy.

Potentiometric methods with ion-selective membrane electrodes (ISMEs) can provide valuable and straightforward means of assaying fentanyl in pharmaceutical formulations because of the possibility to determine directly and without any prior separation the active ions in the solution. ISMEs' low cost, ease of use and maintenance, and the simplicity and speed of assay procedure, and the reliability of the analytical information make them very attractive for the assay of pharmaceutical products. With previous preconcentration of the sample, the detection limits of potentiometric techniques using ion-selective membrane electrodes may equal those of RIA, GLC, HPLC and LC–MS, etc. Although ISMEs have been widely used in pharmaceutical analysis [40–43], no electrodes responsive to fentanyl have so far been described. For this reason, we decided to investigate the response characteristics of a poly (vinyl chloride) membrane electrode with dibutyl phthalate as plasticizer based on ion association of fentanyl and phosphotungstate as electroactive material for the determination of fentanyl citrate in injections. The results agreed fairly well with those obtained by the United States Pharmacopoeia (USP) standard procedure [44]. The proposed electrodes were flexible and inexpensive analytical devices for the determination of the quality and uniformity of pharmaceutical formulations.

2. Experimental

2.1. Reagents

All chemicals were analytical reagent grade and solutions were prepared with deionized water (conductivity >1 μS cm^{-1}). Phosphotungstic acid was obtained from Aldrich, poly (vinyl chloride) (PVC, high molecular weight) from Fluka, dibutyl phthalate (DBP), dibutyl sebacate (DBS) and bis (2-ethylhexyl) adipate (BEA) from Sigma, dioctyl phthalate (DOP), dimethyl phthalate (DMP), dinonyl phthalate (DNP), tributyl phosphate (TBP), tetrahydrofuran (THF), ammonium acetate, methanol, acetonitrile, and glacial acetic acid were obtained from local chemicals supplier. The fentanyl citrate reference standard was obtained from the National Anesthesia Drug Laboratory, Beijing, People's Republic of China. Its characteristic was consistent with the USP [44]. The fentanyl citrate injections (0.1 mg per 2 cm^3 fentanyl citrate sterile solution) were supplied by the Hubby Yea Ltd. Co., Hubby, People's Republic of China. A 1×10^{-2} mol dm^{-3} fentanyl citrate stock solution was prepared by dissolving 2.6431 g of pure anhydrous fentanyl citrate reference standard in 500 cm^3 0.1 mol dm^{-3} citrate–NaOH buffer (pH 4.0). By appropriate dilution with the citrate–Na_2HPO_4 buffer, a series of standard solutions in the concentration range 1×10^{-7}–1×10^{-3} mol dm^{-3} were obtained.

2.2. Apparatus

All EMF measurements were made with a pHS-3C Digital pH meter (Kai Li Scientific Instrument Ltd Co, Xiaoshan, People's Republic of China). The external reference electrode was a model 801 double-junction saturated calomel electrode with outer bridge electrolyte (Jiangsu Electroanalytical Instrument Factory, Jiangsu, Peoples Republic of China). A model 65-1 glass electrode (Kangling Optical and Electrical Tech Ltd. Co., Shanghai, People's Republic of China) was used for pH measurement.

ALC/GPC model 201 HPLC (Waters, USA) and DL-800 Chromatographic Working Station (Dalian Elite Scientific Instruments Co Ltd., Liaoning, People's Republic of China) were employed for the determination injections of fentanyl citrate by USP standard procedure [44].

2.3. Construction of the electrode

The ion-association complex was prepared by mixing stoichiometric amounts of 10^{-2} mol dm^{-3} solution of phosphotungstate with an equimolar unbuffered solution of fentanyl citrate. The precipitate was filtered and washed with

deionized water for 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 desiccator. The master membrane was prepared according to Craggs [45]. The PVC-membrane composition was 0.5 wt.% fentanyl–silicotungstate ion-associate complex, 49.75 wt.% plasticizer and 49.75 wt.% PVC. The electrode body was filled with an inner filling solution containing 10^{-4} mol dm^{-3} fentanyl citrate (saturated with AgCl). This electrode was preconditioned overnight by soaking it in a 10^{-3} mol dm^{-3} fentanyl citrate solution. 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^{-4} mol dm^{-3} fentanyl citrate||Ag/AgCl. The electrode was washed with deionized water and blotted with tissue paper between measurements.

2.4. Standard preparation

Dissolved an accurately weighed quantity of fentanyl citrate reference standard in deionized water, and diluted quantitatively with deionized water to obtained a solution having a known concentration of about 80 μg cm^{-3} [44].

2.5. Assay preparation of injection

Diluted the injection with deionized water so that each cm^3 contained the equivalent of about 50 μg of fentanyl [44].

2.6. Direct potentiometry

Aliquots of 10 cm^{-3} of 1×10^{-7}–1×10^{-2} mol dm^{-3} fentanyl citrate standard solutions were transferred into 25 cm^3 beakers. The PVC fentanyl-phosphotungstate membrane electrode in conjunction with a double-junction saturated calomel electrode were placed into well stirred 10 cm^3 of standard solutions in the order of 1×10^{-7}–1×10^{-2} mol dm^{-3} and potentials were recorded. The equation for the calibration curve was $E = (468.4 \pm 1.6) + (55.9 \pm 0.4)\log C$. The measured potential was plotted against the logarithm of the fentanyl citrate concentration. With the mean potential of five measurements the unknown concentration could be derived from the regression equation of calibration graph.

2.7. Standard addition method

A PVC fentanyl-phosphotungstate membrane electrode in conjunction with a double-junction saturated calomel electrode were immersed into a sample of 10 cm^3 with unknown concentration (ca. 10^{-4} mol dm^{-3}) for 30 s and the equilibrium potential of E_1 was recorded. Then 0.1 cm^3 of 1×10^{-2} mol dm^{-3} of fentanyl citrate standard was added into the testing solution and the equilibrium potential of E_2 was obtained after 30 s. From the change of ΔE ($E_2 - E_1$) one can determine the concentration of the testing sample [46].

2.8. HPLC measurement

The USP measurement was performed with a μBondapak C18 column (4.6×250 mm). Equal volumes (about 25 mm^3) of the standard preparation and the assay preparation of injection were injected into the chromatograph separately. The chromatograms were recorded and the responses for the major peaks were measured. The quantity, in μg, of fentanyl ($C_{22}H_{28}N_2O$) in each cm^3 of the injection was calculated by the formula:

$$\left(\frac{336.48}{528.61}\right) CD \left(\frac{r_U}{r_S}\right),$$

in which 336.48 and 528.61 are the molecular weights of fentanyl and fentanyl citrate, respectively, C is the concentration, in μg cm^{-3}, of fentanyl citrate reference standard in the standard preparation, D is the dilution factor used to obtain the assay preparation, and r_U and r_S are the peak responses for the fentanyl peak obtained from the assay preparation and the standard preparation, respectively [44].

3. Results and discussion

The critical response characteristics of a PVC fentanyl-phosphotungstate membrane electrode with DBP plasticizer at 25 °C were given in Table 1. Calibrations were made at a constant pH and ionic strength using 0.1 mol dm^{-3} citrate–NaOH buffer (pH 4.0). The electrode displayed a linear response for aqueous fentanyl citrate solutions over the concentration range 1×10^{-5}–1×10^{-2} mol dm^{-3}. The calibration slopes were 55.9 ± 0.4 mV. The lower detection limit observed for the fentanyl-phosphotungstate membrane electrodes was determined according to the IUPAC recommendations and was found to be 5.43×10^{-6} mol dm^{-3} fentanyl citrate (1.827 μg cm^{-3} fentanyl) [46]. The potential readings were stable and consistent to ± 1.2 mV within the same day and were reproducible to within ± 2 mV in a 1×10^{-4} mol dm^{-3} fentanyl citrate solution for 4 h continuous use. The stability of the electrode response was checked over a period of 3 months. The time required for the electrode to reached 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 (R.S.D.) values as in Table 1.

The major component of a membrane for ISME was the solvent (plasticizer), which ensured the mobility of the free and complex ionophore, set the dielectric constant, and provided suitable mechanical property of the membrane. As a result, the plasticizer would highly influence the selectivity, measuring range, detection limit and the formation of ion-pairs of ISME [47–50]. As shown in Fig. 1, seven plasticizers were tested by electrode to evaluate the effect of plasticizer on the response. Among seven plasticizers being investigated, the best response characteristics of electrodes were obtained from plasticizer DBP. Meanwhile, the electrodes plasticized with DBP exhibited wide and steady pH applicability. Besides, the selectivity of the electrode plasticized with DBP was found better than that of other plasticizers. To our knowledge, this may be due to the DBP had preferable polarity and lipophilicity suitable for fentanyl-selective membrane electrode. Considering the selectivity, measuring range, detection limit, pH applicability and steady response characteristics of the electrode, DBP was

Table 1
Response characteristics of the fentanyl-selective PVC membrane electrode based on fentanyl-phosphotungstate ion-association complex with DBP plasticizer

Parameter	Response
Slope (mV per decade)[a]	55.9 ± 0.4
Intercept E (mV)[b]	468.4 ± 1.6
Correlation coefficient, r	0.9992
Linear range (mol dm^{-3})	1×10^{-5} to 1×10^{-2}
Lower detection limit (mol dm^{-3})	5.43×10^{-6}
Equation for the calibration curve	$E = (468.4 \pm 1.6) + (55.9 \pm 0.4)\log C$

Measurements were made in 0.1 mol dm^{-3} citrate–NaOH buffer at pH 4.0, 25 °C.

[a] S.D. of average slope values for multiple calibration ($n = 45$).

[b] S.D. of values recorded over a period of 3 months ($n = 45$).

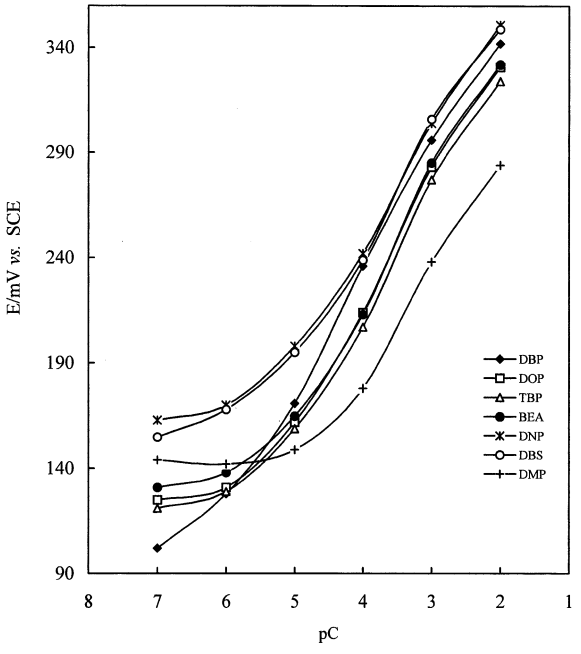

Fig. 1. The effect of plasticizers on potentiometeric response at 25 °C.

Table 2
Potentiometric selectivity coefficients $K_{I,J}^{Pot}$ for the PVC fentanyl-phosphotungstate membrane electrode with DBP plasticizer

Interferent	$K_{I,J}^{Pot}$	Interferent	$K_{I,J}^{Pot}$
$NaHSO_3$[a]	2.2×10^{-3}	DL-alanine[e]	5.6×10^{-3}
Na_2CO_3[b]	1.1×10^{-3}	Potassium oxalate[f]	1.6×10^{-3}
Benzoic acid[b]	2.3×10^{-3}	NaCl[g]	1.3×10^{-3}
Picric acid[c]	1.3×10^{-3}	Thebaine [g]	1.8×10^{-1}
$(NH_4)_2SO_4$[c]	9.4×10^{-4}	Caffeine[g]	1.6×10^{-3}
$Hg(NO_3)_2$[c]	3.8×10^{-5}	Cinchonine[g]	6.5×10^{-2}
Urea[d]	1.5×10^{-3}	Theophylline[g]	1.9×10^{-3}
Glucose[d]	2.2×10^{-3}	Morphine HCl[g]	1.5×10^{-3}
DL-cystine[e]	2.5×10^{-3}	Procaine[g]	1.7×10^{-2}

The concentrations of fentanyl citrate and the interferents were kept at a level of 1×10^{-3} mol dm^{-3} in solutions of the same pH and ionic strength (0.1 mol dm^{-3} citrate–NaOH buffer of pH 4.0) at 25 °C.

[a] Anti-oxidants in the normal injections.
[b] Preservative agents in the normal injections.
[c] Precipitating agents of sample preparation.
[d] Endogenous substances of urine.
[e] Amino acids.
[f] Anticoagulants of blood sample preparation.
[g] Structural analogues.

chosen for construction of the electrode and following study.

The pH dependence of the potentials of the electrode was investigated by observing the changes in the potential readings with pH of the unbuffered solutions (1×10^{-6}–1×10^{-2} mol dm^{-3} fentanyl citrate solution) after addition of small volumes of 3 mol dm^{-3} HCl and/or 3 mol dm^{-3} NaOH. It was found that the fentanyl-sensitive membrane electrode based on fentanyl-phosphotungstate ion-association complex showed virtually no pH response over the range of 1.0–7.0 pH units. That means the protonation form of fentanyl could be maintained in the range of 1.0–7.0 pH units. Decrease in the potentials above pH 7.0 would be presumably due to the formation of the deprotonated fentanyl species and precipitation of free fentanyl base in the test solutions, which was not sensed by the electrode, respectively.

Potentiometric selectivity coefficient defines the ability of an ion-selective electrode to distinguish a particular ion from others. It is one of most important characteristic of an ion-selective electrode, as it often determines whether a reliable measurement in the target sample is possible. Considered the further utilization of the fentanyl-selective PVC membrane electrode in analyzing biological sample, such as urine and blood, some substances might exist in the procedure of the sample preparation were selected. The interference of common inorganic cations, antioxidants and preservative agents in the normal injections, precipitating agents of sample preparation, endogenous substances of urine, amino acids, anticoagulants of blood sample preparation, and some structural analogues on selectivity of proposed electrode were studied by the separated solution method (SSM) recommended by the IUPAC [46]. The concentrations of fentanyl citrate and the interferents were kept at a level of 1×10^{-3} mol dm^{-3} in solutions of the same pH and ionic strength (0.1 mol dm^{-3} citrate–NaOH buffer of pH 4.0) at 25 °C. The potentiometric selectivity coefficients ($K_{I,J}^{Pot}$) listed in Table 2 showed that the proposed electrode exhibited reasonable selectivity towards fentanyl citrate. There was no significant interference from most of the tested substances with the exception of thebaine that was of slight interference.

The proposed electrode was employed for the assay of the fentanyl citrate content in injections by the standard addition method. The results of the potentiometric methods compared with the USP standard procedure were shown in Table 3. As could be seen from Table 3, the results correlated well with those obtained by the USP standard procedure.

4. Conclusions

Compared with the already existing procedures for the determination of fentanyl, such as RIA [1–5,11,16,28], RRA [6–8], ELISA [9–13], FIA [14], GC [15–20], CGC [21–23], GC–MS [4,21,24–28], GLC [29], and HPLC [30–36,38], etc. which required special instrumentation, reagents, precautions and experience, the proposed fentanyl-selective PVC membrane electrode

Table 3
Comparisons of mean values of potentiometric method and USP standard method for the assay of fentanyl citrate in injection

Sample (0.1 mg per 2 cm^3)	Potentiometric method		USP standard method [44]	
	Recovery (% of nominal value)[a]	R.S.D. (%)	Recovery (% of nominal value)[a]	R.S.D. (%)
1	97.94	0.74	98.46	0.66
2	99.01	1.06	98.69	0.68
3	98.45	1.00	98.60	0.76
4	98.93	1.08	98.56	0.90
5	99.81	0.86	98.43	0.91

[a] All values were the average of five determinations.

based on fentanyl-phosphotungstate ion-association complex exhibited the advantages of simple design and operation, reasonable selectivity, fast response and sufficient accuracy for the determination of fentanyl citrate in pharmaceutical formulations.

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