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Use of Sodium Tetraphenyl Boron for Fabrication of Potentiometric Membrane Sensor for the Assay of Olanzapine in Pharmaceuticals and Human Urine

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ABSTRACT

Olanzapine (OLP), chemically known as 2-Methyl-10-(4-methyl-piperazin-1-yl)-4H-3-thia-4,9-diaza-benzo[f]azulene, is an atypical antipsychotic drug. It is used for the treatment of schizophrenia and bipolar disorder. A new simple and selective membrane based potentiometric sensor was developed for potentiometric determination of olanzapine. The membrane was constructed using an ion-pair of OLP and sodium tetraphenyl boron in dioctyl phthalate and PVC. The membrane provides good linear Nernstian response covering relatively wide concentration range of 4×10^{-6} - 1×10^{-2} M OLP over pH range of 2.6-7.8. The detection limit for the developed sensor was founded as 2.02×10^{-6} M. The response time of developed sensor is <10 s for the range of determination. The sensor showed good selectivity for OLP in the presence of various cations, anions and other organic molecules. The membrane was successfully applied in direct potentiometric determination of OLP in tablets. The percentage recovery of OLP, ranged from 96.2 to 99.68% with a mean standard deviation <5% indicates the adoptability of sensor for the direct estimation of OLP in pharmaceuticals. The developed sensor was used to determine OLP in spiked human urine sample and the satisfactory results were obtained.

Keywords: Olanzapine; Membrane Sensor; Assay; Pharmaceuticals; Spiked Human Urine

1. Introduction

Olanzapine (OLP), chemically known as 2-Methyl-10-(4-methyl-piperazin-1-yl)-4H-3-thia-4,9-diaza-benzo[f]azulene (**Figure 1**), is the most commonly prescribed second generation neuroleptic agent for the treatment of schizophrenia and other psychotic disorders.

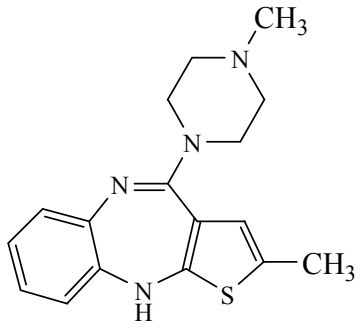

Figure 1; Structure of OLP**.**

In the literature titrimetry[1-3], visible spectrophotometry[3-10], kinetic spectrophotometry[11], UV-spectrophotometry[2,12], capillary zone electrophoresis and linear voltammetry[12] and high-performance thin layer chromatography (HPTLC)[13-15] have been reported for determination of OLP in pharmaceuticals. Several liquid chromatographic methods[16-33] have also been reported for the assay of OLP in pharmaceuticals and biological materials.

Research in the field of development of potentiometric sensors is gaining an increasing number of attention and numerous potentiometric sensors have been developed for the determination of species in the areas of chemical, pharmaceutical and biomedical analyses[34-45]. Potentiometric sensors offers advantages as their use to quantify the compounds since they neither need sophisticated instrument nor relying on stringent experimental conditions.

As presented above literature did not reveal the report for determining OLP with potentiometric sensor.

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Hence, an attempt has been made to develop a potentiometric membrane sensor for the determination of OLP in pharmaceuticals and spiked human urine. The membrane sensor has been fabricated by preparing ion pair complex of OLP with sodium tetraphenylboron using dioctyl phthalate and polyvinyl chloride. Different parameters were optimized to improve the selectivity of membrane to determine OLP with accurate and precise results. The fabricated sensor has been used to develop a new potentiometric method to determine OLP in pharmaceuticals and spiked human urine.

2. Experimental

2.1 Apparatus

Potentials were measured with Labman Micrprocessor based potentiometer (Ahmedabad, India). An Elico (Mumbai, India) pH meter was used to measure the pH of solutions.

2.2 Reagents and materials

All reagents used were of analytical grade. Sodium tetraphenyl boron (NaTPB), dioctyl phthalate (DOP), polyvinyl chloride (PVC), tetrahydrofuran (THF), sucrose, fructose, glucose, maltose, starch, lactose, glycine, sodium fluoride, calcium chloride, nickel chloride, potassium chloride, ammonium chloride, cadmium chloride, cobalt chloride, sodium acetate (NaOAc) and sulphuric acid (H_2SO_4; 98% v/v, Sp. Gr 1.84) were purchased from Merck, Mumbai, India. The drug sample of OLP, certified to be 99.88% pure was obtained as gift from Cipla India Ltd, Mumbai, India. Three brands of tablets, namely, Oleanz (2.5 and 7.5 mg OLP per tablet) and Olanex (10 and 15 mg OLP per tablet) marketed by Sun Pharmaceuticals Industries Ltd, Mumbai, India, and Ranbaxy Laboratories Ltd (Solus), Haryana, India, respectively, were purchased from local commercial sources. A fresh urine sample was collected from a 25 year old Men volunteer.

2.3 Standard solutions

A stock solution of 0.01M OLP was prepared by dissolving and diluting the required quantity of pure drug in 0.1M H_2SO_4 in a volumetric flask. All dilutions were made with the same solvent to prepare calibration standards of OLP. Solutions of 0.01 M NaTPB and 2 M NaOAc were prepared by dissolving calculated amount the compound in distilled water. Solutions of 0.001M each of sucrose, fructose, glucose, maltose, starch, lactose, glycine, sodium fluoride, calcium chloride, nickel chloride, potassium chloride, ammonium chloride, cadmium chloride and cobalt chloride were prepared in water.

3. General Procedures

3.1 Sensor fabrication

An ion-pair complex of OLP and NaTPB was prepared by mixing 20 mL each of 0.01M solutions. The mixture was stirred for 20 minutes and filtered the obtained yellowish white precipitate. The precipitate was washed with deionized water and dried overnight at room temperature.

The membrane was prepared by mixing 15 mg of ion-piar complex of OLP and NaTPB, 50 mg of DOP and 65 mg of PVC, and dissolving in 5 mL of THF. The content was poured into a Petri Dish of 5 cm diameter and kept for slow evaporation for 24 hours. The master membrane with thickness 0.13 mm was mounted to the softened end of the PVC tube with the aid of adhesive prepared using PVC and THF. A 20 mL of 0.01M OLP solution with 0.25 mL of 0.5 M KCl was filled into the tube. Pure copper wire of 2.0 mm diameter and 15 cm length was tightly insulated leaving 1.0 cm at one end and 0.5 cm at other end for connection. One terminal of the wire was inserted into the tube and the other terminal was connected to the potentiometer. Silver-AgCl electrode was allied with the membrane as reference electrode. The membrane was conditioned by soaking it into a solution of ion-pair atleast for 24 hours.

3.2 Preparation of calibration curve

Into a series of 25 mL volumetric flasks varying aliquots of 0.01 M OLP standard solutions equivalent to 4×10^{-6} - 1×10^{-2} M OLP were placed by means of a microburet, the pH were adjusted to ~4.0 with 2 M NaOAc and the final volume was brough to the mark and the contents were mixed well. The potential of each solution was measured by using Ag/AgCl reference electrode and membrane electrode.

The calibration graph of measured potential *versus* –log [OLP] was prepared. The concentration of the unknown was found by using calibration graph or regression equation derived using potential and –log [OLP] data.

3.3 Procedure for interference study

In a 10 ml volumetric flask 2 ml of 0.01M drug

solution and 2ml of 1mM solution of interferent was taken. The solution after adjusted to pH 4 and diluting to mark the potentials of each were measured using the electrochemical cell assembled for preparation of calibration curve.

3.4 Procedure for tablets

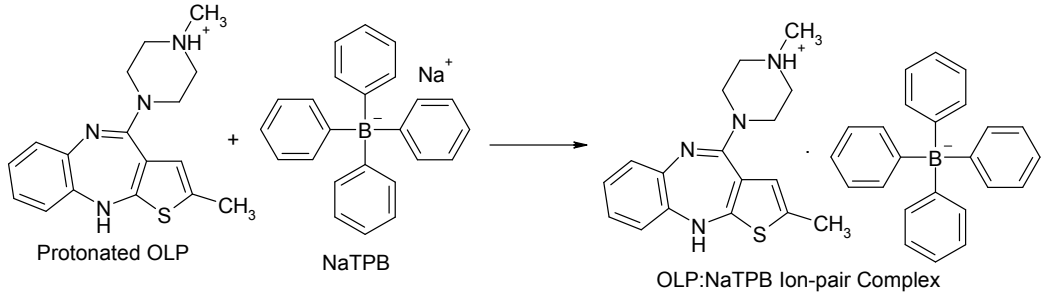
Twenty tablets were weighed and ground to a fine powder. Portion of the powdered tablet equivalent to 78.11 mg of OLP was transferred in to a 25 ml volumetric flask and shaken with 20 ml of 0.1M H_2SO_4 for 20 minutes. The content after diluting to the mark with the same solvent was mixed and filtered through Whatmann No. 41 filter paper. A suitable aliquot was used to measure the potential by following the procedure as described under procedure for preparation of calibration curve. The concentration of OLP was calculated using the calibration curve or regression data.

3.5 Procedure for spiked human urine

In a 10ml volumetric flask 1ml of 1:10 urine and 2ml of 0.01M OLP solution were taken. The volume was brought to the mark and mixed well. After bringing the solution to the optimum pH of 4 the potential of the solution was measured using OLP-NaTPB sensor and Ag-AgCl reference electrode. The concentration of OLP in the solution was calculated using the calibration curve or regression data.

4. Results and discussions

The development and validation of ion-selective electrodes using membranes is of interest for pharmaceutical analysis because they offer the advantages of simplicity of fabrication and operation, rapid response time, fair detection limits, acceptable selectivity, accuracy and precision, applicable to the detection of wide concentration range to colored and turbid solutions, and probability to automate and computerize. The acidic solution of OLP reacted with sodium tetraphenylborate and formed a stable 1:1 water insoluble yellowish ion association complex, with low solubility product and suitable grain size precipitate. The probable structure of OLP and NaTPB is proposed and given in Scheme 1. This precipitate was used to fabricate the membrane consisting of ion-pair, DOP and PVC.



Scheme 1. Reaction pathway for formation of OLP-NaTPB ion-pair complex

Different experimental variables such as pH, soaking time, response time, stability and effect of ions etc, were studied by measuring the potential of the OLP solution of known concentration using the developed sensor.

The optimum pH range of the sensor was found to be 2.6 to 7.8 and at which the potential measured for each solution of OLP of any concentration within the linear range were almost constant. There is higher and lower potential values were observed at pH lesser than 2.6 and at higher than 7.8 (**Figure 2**).

The developed sensor was subjected to measure the potential of OLP solution in the presence of various organic and inorganic compounds, cations and anions by spiking the solutions of 0.001M each of sucrose, fructose, glucose, maltose, starch, lactose, glycine, sodium fluoride, calcium chloride, nickel chloride, potassium chloride, ammonium chloride, cadmium chloride or cobalt chloride into 6.0×10^{-5} M OLP solution. This was done in accordance to the IUPAC guidelines[46,47]. None of the added species showed effect on the potential. This confirmed that the sensor is selective for the determination of OLP in the presence of such charged or neutral species.

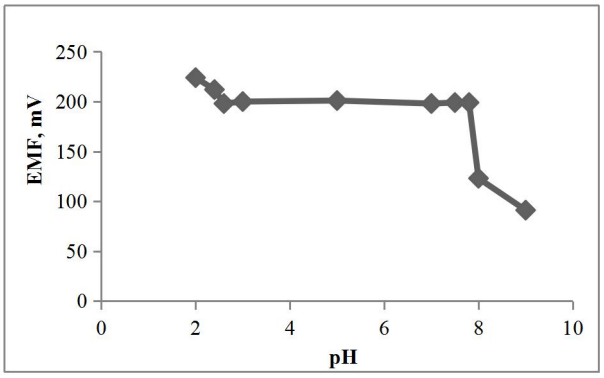


Figure 2; Effect of pH on EMF (6.0×10^{-5} M OLP).

5. Validation results

5.1 Linearity and sensitivity

The electrochemical response parameters of developed OLP-NaTPB sensor was evaluated according to IUPAC recommendations[46,47] using the membrane working electrode and Ag-AgCl reference electrode. The results showed that the sensor provides rapid, stable and linear response for the OLP concentration range 4×10^{-6} - 1×10^{-2} mol L^{-1}. The calibration graph (**Figure 3**) obtained Nernestian response with slope of 60±1 mV/decade. This confirms the sensor obey the linearity equation of y = mx + c; where y, c and m refers to E (mV), E^o (mV) and slope (mV/decade) of the curve, respectively. Stable potentiometric readings were obtained with variations within ±5 mV during the period of 11 weeks. The limit of detection determined from the intercept of the two lines of the calibration graph is 2.02×10^{-6} mol L^{-1}. These results are summarised in **Table 1**.

5.2 Accuracy and precision

Intra- and inter-day precision were evaluated by analysing pure OLP solutions at three different concentrations in seven replicates during the same day and five replicates during different days. The amounts of OLP found in each case were computed. Precision for each set of results was assessed by calculating RSD values. The accuracy in the measurement was evaluated by calculating the amount of OLP for respective potentials of drug solution. The relative error (RE), the metric for accuracy, is calculated for each concentration of OLP found. The percent relative error which is an index of accuracy, ranged from 0.2 to 2.0 indicated acceptable accuracy. The obtained RSD values ranged between 2.81 and 4.14% indicated satisfactory precision of the results. These results are presented in **table 2**.

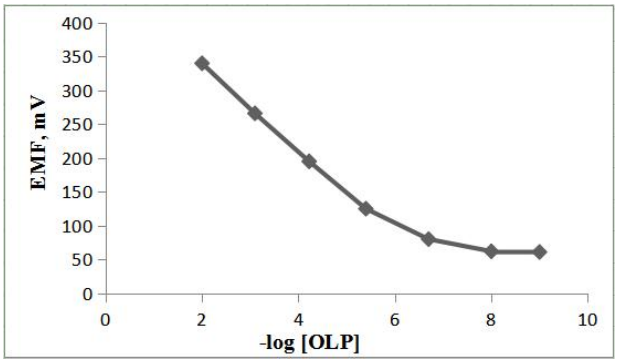


Figure 3; Calibration curve.

Parameters	Values
Linear range, mol L^{-1}	4×10^{-6} - 1×10^{-2}
Limit of detection (LOD), mol L^{-1}	2.02×10^{-6}
Limit of quantification (LOQ), mol L^{-1}	3.15×10^{-6}
Slope (m), mV/decade	60±1
Intercept (b), mV	384.8
Correlation coefficient (r)	0.9996
Response time, s	<10
Working pH range	2.6-7.8
Life span of sensor, Weeks	11

Table 1. Electrochemical characteristics of the membrane sensor

5.3 Robustness and ruggedness

The robustness of an analytical procedure is a measure of its capacity to remain unaffected by small, but deliberate variations in method parameters and provides an indication of its reliability during normal usage. At the deliberate varied experimental conditions [pH: 4.0(±2) and temperature: 25±2 ^{O}C], the %RSD, remained unchanged to the actual values. The RSD values ranged from 2.15 to 3.42% confirmed the robustness of the proposed method. In method ruggedness, the analyses with different potentiometers, at different day by different analyst were performed. Such variations did not yield any appreciable change in the measurement. The inter-instrumental and inter-analysts RSD values of <3.4% declares the potentiometric sensor is robust in nature.

OLP taken, mmol L-1	Intra-day (n = 7)			Inter-day (n = 5)		
	OLP Found, mmol L^{-1}	% RE	% RSD	OLP Found, mmol L^{-1}	% RE	% RSD
2.00	1.96	2.00	2.81	2.04	2.00	3.45
5.00	5.03	0.60	2.92	5.03	0.60	4.14
10.00	9.92	0.80	2.99	10.02	0.20	2.86

%RE: Percent relative error; %RSD: Percent relative standard deviation.

Table 2. Results of accuracy and precision study

5.4 Application to tablets

A 5 mL of 0.01M OLP solution of tablets extract prepared under 'procedure for tablets' was subjected to analysis by the optimized procedure. The mean measured potential of the tablets extract was found to be equivalent to that of the pure drug and the results were compared with those of a reference method[2]. The method consisted of the visual titration of the acetous solution of the tablet with acetous perchloric acid in acetic acid medium. The accuracy and precision were evaluated by applying Student's t- test and variance ratio F- test, respectively. The calculated t- and F- values at 95% confidence level did not exceed the tabulated values and this confirms that there is no significant difference between the reference and proposed method. The mean percent recovery of OLP from tablets was found as 98.5 with RSD value of less than 3%. These data are presented in **Table 3**.

Tablet analyzed	Label claim, mg/tablet[a]	Found[b] (Percent of label claim ±SD)	
		Reference method	Proposed method
Oleanz-7.5	7.5	99.17±0.76	98.00±1.21 t = 1.87 F = 2.53
Olanex-10	10	97.15±1.16	99.00±1.21 t = 2.47 F = 1.09

[a]Amount in mg per tablet; [b]mean value of 5 determinations.

Table 3. Results of analysis of tablets by the proposed method and statistical comparison of the results with the reference method

5.5 Recovery study

The accuracy of the sensor was further assessed by following a standard addition procedure. The solutions were prepared by spiking pure drug into a pre-analyzed tablet powder at three different levels and potential measured using the sensor. To a 3 mL of 0.01M OLP from tablet five replicate each of 1.5, 3 and 4.5 mL of 0.01 OLP from pure drug were spiked, pH adjusted and after diluting to 25 mL, and the potential measured. For obtained potentials the amounts of OLP were calculated. The recovery of the known amount of added OLP was calculated. The percentage recovery of OLP from tablets, presented in table 4, ranged from 95.0 to 105.0% with less than 4% of RSD revealed that good and acceptable recovery values were obtained.

Tablet Studied	OLP in tablet, mmol L^{-1}	Pure OLP added, mmol L^{-1}	Total found, mmol L^{-1}	Pure OLP recovered (Percent±SD*)
Oleanz-2.5	1.20 1.20 1.20	0.60 1.20 1.80	1.78 2.36 3.02	96.70±0.87 96.70±1.00 101.1±3.44
Oleanz-7.5	1.20 1.20 1.20	0.60 1.20 1.80	1.83 2.41 2.96	105.0±2.33 100.8±1.87 97.78±3.21
Olanex-10	1.20 1.20 1.20	0.60 1.20 1.80	1.79 2.34 3.03	98.33±0.97 95.00±1.21 101.7±2.22
Olanex-15	1.20 1.20 1.20	0.60 1.20 1.80	1.82 2.43 3.08	103.3±2.32 102.5±1.10 104.4±2.21

*Mean value of three measurements

Table 4. Results of accuracy assessment by recovery test for tablets

5.6 Spiked human urine analysis

From the analysis of urine sample spiked with known amount of OLP solution the percent recovery of

OLP were ranged from 94.12 to 97.22% with RSD of <5% indicates that the endogenous substances did not interfere while measuring the potential of the solution of OLP in presence of urine. This inference paved the applicability of the procedure using the developed sensor for physiotherapeutic administration of OLP.

6. Conclusions

This is the first paper describing the fabrication of membrane sensor and its application to determine olanzapine in pharmaceuticals and spiked human urine. The sensor provides fast and linear Nernestian response over a wide range of olanzapine concentration. The sensor has been successfully used in the determination of drug content in pure state, brands of tablets and from spiked human urine with acceptable recovery. The results obtained were highly accurate and precise with good agreement to consider the sensor for its use as tool to determine olanzapine in routine quality control laboratories. The assembly present simple, low cost and selective method for direct determination of olanzapine in aqueous media without prior separation.

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