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

**RAJENDRA PRASAD NAGARAJU**

PG Department of Chemistry, JSS College of Arts, Commerce & Science, B N Road, Mysuru, Karnataka, India

**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](https://en.wikipedia.org/wiki/Schizophrenia" \o "Schizophrenia) and [bipolar disorder](https://en.wikipedia.org/wiki/Bipolar_disorder" \o "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. 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 (H2SO4; 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 H2SO4 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 H2SO4 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), Eo (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 ᴼC], 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  5.00  10.00 | 1.96  5.03  9.92 | 2.00  0.60  0.80 | 2.81  2.92  2.99 | 2.04  5.03  10.02 | 2.00  0.60  0.20 | 3.45  4.14  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/tableta | Foundb (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 |

aAmount in mg per tablet; bmean 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.

**Acknowledgement**

Author thanks Cipla India Ltd, Mumbai, India, for gifting pure olanzapine sample. The author is indebted to UGC, SWRO, Bengaluru, India, for financial assistance in the form of Minor Research Project Grant of Award No. 1495-MRP/14-15/KAMY013/UGC-SWRO, dated 04-02-15, to pursue this research work. The authors are grateful to the Principal of JSS College of Arts, Commerce and Science, B N Road, Mysuru, India, for providing the facilities to pursue this work.

**References**

1. K. Basavaiah, N. Rajendraprasad and K.B. Vinay, “Microtitrimetric determination of drug content of pharmaceuticals containing olanzapine in non-aqueous medium”, Chemical Industry and Chemical Engineering (Quarterly), vol. 15, pp. 77-81, 2009.
2. S. Firdous, T. Aman and A. Nisa, “Determination of olanzapine by UV spectrophotometry and non-aqueous titration”. Journal of Chemical Society of Pakistan, vo.l 27, pp.163-167, 2005.
3. K. Basavaiah and A.M.A. Sameer, “Sensitive and selective methods for the determination of olanzapine in pharmaceuticals using n-bromosuccinimide and two dyes”, International Journal of ChemTech Research, vol. 2, pp.660-668, 2010.
4. A. Krebs, B. Starczewska, H. Puzanowsha-Tarasiewicz and J. Sledz, “Spectrophotometric determination of olanzapine with N-bromosuccinimide and cerium(IV)sulphate”, Analytical Sciences, vol. 22, pp. 829-833, 2006.
5. A. Jasinska and E. Nalewajko, “Batch and flow-injection methods for the spectrophotometric determination of olanzapine”, Analytica Chimica Acta, vol. 508, pp. 165-170, 2004.
6. N. Rajendraprasad, K. Basavaiah, K. Tharpa and K.B. Vinay, “Quantitative determination of olanzapine in tablets with visible spectrophotometry using cerium(IV)sulphate and based on redox and complexation reactions”, Eurasian Journal of Analytical Chemistry, vol. 4, pp. 193-203, 2009.
7. N. Rajendraprasad and K. Basavaiah, “Highly sensitive spectrophotometric determination od olanzapine using Cerium(IV) and iron(II) complexex of 1,10-phenanthroline and 2,2’-bipyridyl”, Journal of Analytical Chemistry, vol. 65, pp. 482-488, 2010.
8. K. Basavaiah, A.M.A. Sameer and, K.B. Vinay, “New extractive spectrophotometric methods for the determination of olanzapine in pharmaceutical formulatins using bromocresol green”, Jordan Journal of Chemistry, vol. 5, pp. 101-117, 2010.
9. N. Rajendraprasad and K. Basavaiah, “Determination of olanzapine by spectrophotometry using permanganate”, Brazilian Journal of Pharmaceutical Sciences, vol. 45, pp. 539-550, 2009.
10. K. Basavaiah, K. Tharpa, N. Rajendraprasad, S.G. Hiriyanna and K.B. Vinay, “Spectrophotometric Determination of Antipsychotic Drug Olanzapine in Pharmaceuticals”, Jordan Journal of Chemistry, vol. 4, pp. 65-76, 2009.
11. A.A. Mohamed, “Kinetic and maximum-absorbance spectrophotometric methods for the determination of olanzapine”, Monatshefte fur Chemie/Chemical Monthly, vol. 139, pp. 1005-1010, 2008.
12. M.A. Raggi, G. Casamenti, R. Mandrioli, G. Izzo and E. Kenndler, “Quantification of olanzapine in tablets by HPLC, CZE, derivative spectrometry and linear voltammetry”, Journal of Pharmaceutical and Biomedical Analysis, vol. 23, pp. 973-981, 2000.
13. R.B. Patel, M.R. Patel, K.K. Bhatt and B.G. Patel, “Development and validation of an HPTLC method for determination of olanzapine in formulations”, Journal of AOAC International, vol. 93, pp. 811-819, 2010.
14. C.R. Shah, B.N. Suhagia, N.J. Shah, D.R. Patel and N.M. Patel, “Stability-indicating simultaneous HPTLC method for olanzapine and fluoxetine in combined tablet dosage form”, Indian Journal of Pharmaceutical Sciences, vol. 70, pp. 251-255, 2008.
15. S. Patel and N.J. Patel, “Simultaneous RP-HPLC and HPTLC estimation of fluoxetine hydrochloride and olanzapine in tablet dosage forms”. Indian Journal of Pharmaceutical Sciences, vol. 71, pp. 477-480, 2009.
16. O.V. Olesen and K. Linnet, “Determination of olanzapine in serum by high-performance liquid chromatography using ultraviolet detection considering the easy oxidizability of the compound and the presence of other psychotropic drugs”, Journal of Chromatography B: Biomedical Science Applications, vol. 714, pp. 309-315, 1998.
17. H. Weigmann, S. Härtter, M. Sabine, K. Werner, K. Godehard, D. Gerd and H. Chrostoph, “[Simultaneous determination of olanzapine, clozapine and demethylated metabolites in serum by on-line column-switching high-performance liquid chromatography](http://www.sciencedirect.com/science?_ob=ArticleURL&_udi=B6TG9-43B8HY4-7&_user=10&_coverDate=08%2F05%2F2001&_alid=1534500963&_rdoc=1&_fmt=high&_orig=search&_origin=search&_zone=rslt_list_item&_cdi=5249&_sort=r&_st=13&_docanchor=&view=c&_ct=1&_acct=C000050221&_version=1&_urlVersion=0&_userid=10&md5=066df8b96918ab4c0ec229a399b73f34&searchtype=a)”. Journal of Chromatography B, vol. 759, pp. 63-71, 2001.
18. O.V. Olesen, B. Poulsen and K. Linnet, “Fully automated online determination of olanzapine in serum for routine therapeutic drug”, Therapeutic Drug Monitoring, vol. 1, pp. 51-55, 2001.
19. D. Concetta, M. Gaetana, S. Vincenza and S. Edoardo, “Determination of olanzapine in human-plasma by reversed-phase high-performance liquid chromatography with ultraviolet detection”, Therapeutic Drug Monitoring, vol. 28, pp. 388-393, 2006.
20. L.J. Dusci, L.P. Hackett, L.M. Fellows and K.F. Liett, “Determination of olanzapine in plasma by high-performance liquid chromatography using ultraviolet absorbance detection”, Journal of Chromatography B, vol. 773, pp. 191-197, 2002.
21. M.A. Raggi, G. Casamenti, R. Mandrioli and V. Volterra, “A sensitive high-performance liquid chromatographic method using electrochemical detection for the analysis of olanzapine and desmethylolanzapine in plasma of schizophrenic patients using a new solid-solid phase extraction procedure”, Journal of Chromatography B, vol. 750, pp. 137-146, 2001.
22. M.A. Raggi, G. Casamenti, R. Mandrioli, S. Fanali, D. De Ronchi and V. Volterra, “Determination of the novel antipsychotic drug olanzapine in human plasma using HPLC with amperometric detection”, Chromatographia, vol. 51, pp. 562-566, 2000.
23. M.A. Raggi, R. Mandrioli, C. Sabbioni, N. Ghedini, S. Fanali and V. Volterra, “Determination of olanzapine and desmethylolanzapine in the plasma of schizophrenic patients by means of an improved HPLC method with amperometric detection”, Chromatographia, vol. 54, pp.203-207, 2001.
24. M.A. Saracino, A. Koukopoulos, G. Sani, M. Amore and M.A. Raggi, “Simultaneous high-performance liquid chromatographic determination of olanzapine and lamotrigine in plasma of bipolar patients”, Therapeutic Drug Monitoring, vol. 29, pp.773-780, 2007.
25. C.B. Eap, J.L. Veuthey, D. Guillarme, A. Kottelat, S. Rudaz and E. Choong, “**Therapeutic drug monitoring of seven psychotropic drugs and four metabolites in human plasma by HPLC-MS”,** Journal of Pharmaceutical and Biomedical Analysis, vol. 50, pp. 1000-1008, 2009.
26. M. Josefsson, M. Roman, E. Skogh and M.L. Dahl, “Liquid chromatography/tandem mass spectrometry method for determination of olanzapine and N-desmethylolanzapine in human serum and cerebrospinal fluid”, Journal of Pharmaceutical and Biomedical Analysis, vol. 53, pp. 576-582, 2010.
27. M.A. Saracino, O. Gandolfi, R.O. Dall’Olio, L. Albers, E. Kenndler and M.A. Raggi, “Determination of olanzapine in “rat brain using liquid chromatography with coulometric detection and a rapid solid-phase extraction procedure”, Journal of Chromatography A**,** vol. 1122, pp.21-27, 2006.
28. S.C. Kasper, E.L. Mattiuz, S.P. Swanson, J.A. Chiu, J.T. Johnson and C.O. Garner, “Determination of olanzapine in human breast milk by high-performance liquid chromatography”, Journal of Chromatography B, vol. 726, pp.203-209, 1999.
29. X. Xuejun and T. Zhonghua, “Determination of olanzapine and its tablets by HPLC”, Zhongguo Yiyao Gongye Zazhi, vol. 35, pp. 46-48, 2004.
30. A. Pathak, S.J. Rajput, “Development of stability-indicating hplc method for simultaneous determination of olanzapine and fluoxetine in combined dosage forms”, Journal of Chromatographic Sciences, vol. 47, pp. 605-611, 2009.
31. B.V. Reddy, K.V.N. Suresh Reddy, J. Sreeramulu and G.V. Kanumula, “Simultaneous determination of olanzapine and fluoxetine by HPLC”, Chromatographia, vol. 66, pp. 111-114, 2007.
32. C.R. Shah, N.J. Shah, B.N. Suagia and N.M. Patel, “Simultaneous assay of olanzapine and fluoxetine in tablets by column high-performance liquid chromatography and high-performance thin-layer chromatography”, Journal of AOAC International, vol. 90, pp. 1573-1578, 2007.
33. S.G. Hiriyanna, K. Basavaiah, P.S.K. Goud, V. Dayanidhi, K. Raju and H.N. Pati, “Identification and characterization of olanzapine degradation products under oxidative stress conditions”, Acta Chromatographica, vol. 20, pp. 81-93, 2008.
34. A. Ensafi and A. R. Allafchian. “Novel and selective potentiometric membrane sensor for amiloride determination in pharmaceutical compounds and urine”, [Journal of Pharmaceutical and Biomedical Analysis](http://www.sciencedirect.com/science/journal/07317085" \o "Go to Journal of Pharmaceutical and Biomedical Analysis on ScienceDirect), vol. [47(4-5)](http://www.sciencedirect.com/science/journal/07317085/47/4" \o "Go to table of contents for this volume/issue), pp. 802-806, 2008.

## [G. S. Kanberoglu](http://ieeexplore.ieee.org/search/searchresult.jsp?searchWithin=%22Authors%22:.QT.Gulsah%20Saydan%20Kanberoglu.QT.&newsearch=true), [F. Coldur](http://ieeexplore.ieee.org/search/searchresult.jsp?searchWithin=%22Authors%22:.QT.Fatih%20Coldur.QT.&newsearch=true), [C. Topcu](http://ieeexplore.ieee.org/search/searchresult.jsp?searchWithin=%22Authors%22:.QT.Cihan%20Topcu.QT.&newsearch=true) and [O. Cubuk](http://ieeexplore.ieee.org/search/searchresult.jsp?searchWithin=%22Authors%22:.QT.Osman%20Cubuk.QT.&newsearch=true).  “A Flow‐injection potentiometric system for selective and sensitive determinationof serum lithium level”, [IEEE Sensors Journal](http://ieeexplore.ieee.org/xpl/RecentIssue.jsp?punumber=7361),  [vol. 15(11](http://ieeexplore.ieee.org/xpl/tocresult.jsp?isnumber=7225207)), pp. 6199-6207, 2015.

## H. AlRabiah, A. Al-Majed, M. Abounassif and G.A.E.Mostaf, “Two novel potentiometric sensors for determination of clonidine in some pharmaceutical formulation”, International Journal of Electrochemical Science, vol. 11, pp. 6761 – 6774, 2016.

## M.R. Ganjali, S. Karimi, S.J. Shahtaheri and P. Norouzi, “Determination of clonidine by potentiometry using PVC membrane electrode”, International Journal of Electrochemical Science, vol. 8, pp. 1999-2008, 2013.

### E.M. Del Valle, “[Cyclodextrin and their uses a review](http://www.scirp.org/(S(czeh2tfqyw2orz553k1w0r45))/reference/ReferencesPapers.aspx?ReferenceID=1278990)”, Process Biochemistry. vol. 39, pp. 1033-1046, 2004.

## A.R. Hedges. “Industrial applications of cyclodextrins”, Chemical Reviews, vol. 98, pp. 2035-2044, 1998.

## R. Yang, K.a. Li, K. Wang, F. Zhao, N. Li and F. Liu, “Porphyrin assembly on β-cyclodextrin for selective sensing and detection of a zinc ion based on the dual emission fluorescence ratio”, Analytical Chemistry, vol. 75, pp. 612-621, 2003.

## A.M. El-Kosasy, M. Nebsen, M.K.A. El-Rahman, M.Y. Salem and M.G. El-Bardicy, “Comparative study of 2-hydroxy propyl beta cyclodextrin and calixarene as ionophores in potentiometric ion-selective electrodes for neostigmine bromide”, Talanta, vol. 85, pp. 913-918, 2011.

## M. Trojanowicz, “[Enantioselective electrochemical sensors and biosensors: A mini-review](https://www.sciencedirect.com/science/article/pii/S1388248113004219)”, Electrochemistry Communications, vol. 38, pp. 47-52, 2014.

## S.R. Patil, M. Turmine, V. Peyre, G. Durand and B. Pucci, “Study of β-cyclodextrin/fluorinated trimethyl ammonium bromide surfactant inclusion complex by fluorinated surfactant ion selective electrode”, Talanta vol. 74, pp. 72-77 (2007).

## A.M. El-Kosasy, “Determination of hydroxyurea in capsules and biological fluids by ion-selective potentiometry and fluorimetry”, Journal of AOAC International, vol. 86, pp. 15-21, 2003.

1. K.I. Ozoemena and R-I. Stefan, “Enantioselective potentiometric membrane electrodes based on alpha-, beta- and gamma-cyclodextrins as chiral selectors for the assay of L-proline”, Talanta, vol. 66, pp. 501-504, 2005.
2. IUPAC Analytical Chemistry Division, “Recommendation for Nomenclature of Ion Selective Electrode”, Pure and Applied Chemistry, vol. 66, pp. 2527-2536, 1994.
3. IUPAC Analytical Chemistry Division, “Potentiometric selectivity coefficients of ion selective electrodes”, Pure and Applied Chemistry, vol. 72, pp. 1851-2082, 2000.