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Potentiometric determination of anti–epileptic drugs: A mini review

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ABSTRACT

Epilepsy is a chronic neurological disease and its treatment requires the use of anti–epileptic drugs. The determination of anti–epileptic drugs in pharmaceutical and biological samples is carried out using various analytical methods. Potentiometric methods, which have a very important place in electroanalytical chemistry, are used extensively in the determination of various drugs in biological and pharmaceutical samples. In this study, we reviewed potentiometry–based sensors developed for the determination of anti–epileptic drug molecules in biological and pharmaceutical samples.

1. Introduction

Epilepsy is one of the most common chronic neurological disorders worldwide, and it requires use of anti–epileptic drugs [1]. Anti–epileptic drug treatment can be continued for quite a long time or for life [2]. The concentration of anti–epileptic drugs in various biological samples is extremely important for effective treatment. To date, the determination of anti–epileptic drugs in various pharmaceutical and biological samples has been carried out using various analytical methods such as high–performance liquid chromatography (HPLC), liquid chromatography–mass spectrometry (LC–MS/MS), gas chromatography (GC) and gas chromatography–mass spectrometry (GC/MS) [3–7]. Although these methods give very sensitive and accurate results, they have disadvantages such as the requirement of trained personnel, high cost, high-energy and time consumption as well as not being suitable for on–site detection.

Potentiometry has a very important place in electrochemistry and is based on the measurement of the potential difference between two electrodes, one being the reference and the other working electrode [8]. Potentiometric methods offer multiple advantages including wide linear concentration range, low detection limit, short response time, low cost, long lifetime, low–energy consumption, high selectivity and sensitivity [9–12]. Potentiometric methods have found applications in many areas such as routine laboratory analyses, environmental monitoring, agricultural analysis, medicinal drug analyses, and process control [13–16]. As a result, potentiometric methods can be considered as an alternative to other analytical methods for the quantitative determination of different drugs to be determined in various biological and pharmaceutical samples.

In the study, we reviewed potentiometric sensors which were developed for the determination of anti–epileptic drugs in biological and pharmaceutical samples, and mentioned their performance characteristics.

1.1. Potentiometric methods for the determination of anti–epileptic drugs

A potentiometric biosensor for the analysis of human blood samples was described by Özbek et al. for the determination of valproate (VPA) [17]. The biosensor displayed a linear response over the concentration range of 1.0×10^{-6} to 1.0×10^{-1} M and exhibited a limit of detection of 9.75×10^{-7} M. The proposed biosensor was shown to be useable in the pH range of 4.0–11.0 and to have a fast response time of <10 s. A screen–printed potentiometric sensor with greenness profile evaluation has been developed by Soliman et al. for rapid and direct analysis of sodium valproate in different matrices [18]. This sensor was reported to work in concentration range from 5.96×10^{-5} to 1.0×10^{-2} M. In addition, the sensor had a pH working range from 3.0 to 7.0 and a response time of 5–10 s. The authors reported that the sensor they

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developed can be used for quality control of VPA in different samples with the advantage of real–time, cost–effective and minimal sample preparation. Sabah et al. proposed a solid–state valproate–selective sensor based on conductive polypyrrole (PPy) films for the detection of valproate in pharmaceutical preparations [19]. The developed sensor worked in the concentration range of 4.0×10^{-5} – 4.0×10^{-2} M with a limit of detection of 1.0×10^{-5} M. The selectivity of the sensor in the presence of diverse epileptic drugs (carbamazepine, phenobarbital and phenytoin) and inorganic salts was investigated. The proposed sensor displayed response time of approximately 20 s and lifetime of 4 months. Valproate selective electrodes based on manganese (III) tetraphenylporphyrin [Mn(III)TPP-Cl] as an ionophore have been reported by Santos et al. [20]. Poly (vinly chloride) (PVC) and ceramic membranes (sol–gel) were prepared and their potentiometric performance properties were tested. These electrodes showed lower detection limit of 5.0×10^{-6} M and 1.0×10^{-4} M for PVC and sol–gel membrane, respectively. The prepared valproate–selective electrodes were applied in pharmaceutical samples.

Jalali et al. described the development of a potentiometric sensor for gabapentin (GP) determination in pharmaceutical samples and blood serum [21]. The sensor worked in the concentration range of 1.0×10^{-5} – 5.0×10^{-2} M and had a wide pH working range from 1.8 to 3.2. Abdallah and Ibrahim showed that potentiometric determination of gabapentin in pharmaceutical tablets and spiked plasma samples could be performed using graphene oxide decorated with silver nanoparticles/molecularly imprinted polymer [22]. The sensor displayed a wide linear response over the concentration range of 1.0×10^{-10} – 1.0×10^{-3} M and exhibited a limit of detection of 4.8×10^{-11} M. Response time, pH range and lifetime for this sensor was 15s, 1.5–3.0 and 115 days, respectively.

An ion–selective electrode for the analysis of pharmaceutical formulations was reported by Amorim et al. for the determination of diazepam (DZP) [23]. In the study, (2-hydroxyproyl)-γ-cyclodextrin was used as an ionophore. The potentiometric electrode was observed to be useable in the pH range of 1.9–2.7. In addition, response time of the electrode less than 30s. Another potentiometric determination of diazepam in pharmaceutical samples was performed by Ghorbani et al. using carbon paste sensor prepared with diazepam–tetraphenylborate (DZP–TPB) ion pairs [24]. The sensor exhibited a Nernstian behaviour (58.6 ± 0.2 mV/decade) in concentrations from 1.0×10^{-2} to 5.0×10^{-5} M. Authors showed a fast response time of 5–10 s and independent in the pH range from 3.0 to 5.0.

Potentiometric determination of levetiracetam (LEV) in pharmaceutical samples was performed by Özbek and Isildak using PVC membrane ion–selective electrodes [25]. The authors synthesized the levetiracetam–tetraphenylborate (LEV–TPB) ion pair and used it as an ionophore. This sensor displayed a linear response from 1.0×10^{-5} to 1.0×10^{-1} M with a detection limit of 6.31×10^{-6} M. The sensor displayed a good selectivity in the presence of common ionic species and some anti–epileptic drug.

Alrabiah et al. described the development of ionophore-based PVC membrane potentiometric sensors (β– or γ–cyclodextrin) for the determination of phenobarbitone in pharmaceutical formulations [26]. These sensors showed anionic response (−59.1 and −62.0 mV/decade) over the concentration range of 5.0×10^{-6} – 1.0×10^{-2} M and 8.0×10^{-6} – 1.0×10^{-2} M for β– and γ–cyclodextrin–based sensors, respectively. They showed a fast response time of 25 s and worked in the pH range from 9.0 to 11.0.

Potentiometric determination of lamotrigine (LMT) in human urine and plasma samples was performed by Sadeghi et al. using molecularly imprinted polymers [27]. The developed potentiometric sensor worked in the concentration range of 1.0×10^{-6} – 1.0×10^{-3} M. The sensor works in the pH range of 1.0–5.0 and has a response time of approximately 30 s. Another LMT potentiometric sensor prepared using LMT–dodeca-molybdophosphate (PMA) ion–pair complex was reported in the literature for the determination of LMT in pharmaceutical and urine samples [28]. The sensor exhibited a Nernstian behaviour (57.14 ± 1.0 mV/decade) in concentrations from 5.0×10^{-4} to 9.0×10^{-3} M. The LMT–selective sensor with a detection limit of 1.3×10^{-5} M exhibited a response time < 5s.

Al-Bayati and Karabat reported the development of potentiometric electrode using PVC membrane for the determination of phenytoin (PHY) in pharmaceutical preparations [29]. They used four different plasticizers and investigated their potentiometric performance characteristics. The electrode using di–octylphenylphosphonate (DOPH) as a plasticizer works in the concentration range of 1.0×10^{-5} – 1.0×10^{-1} M. The lifetime of the electrode was shown to be less than 30 days. Another potentiometric sensor for the determination of phenytoin in pharmaceutical preparations and biological fluids was developed by El-Tohamy et al. [30]. They prepared two different types of electrodes: plastic membrane and coated wire. These electrodes worked in the concentration range of 5.0×10^{-3} to 5.0×10^{-6} M and 1.0×10^{-3} to 1.0×10^{-6} M, and had detection limits of 1.3×10^{-6} M, and 2.5×10^{-7} M for electrode plastic membrane and coated wire, respectively. In addition, they observed that the pH ranges of the phenytoin–selective electrodes were 6.0–10.0.

Potentiometric (MIP/PVC/GCE) and voltammetric (MIP/GO/GCE) sensors for selective and sensitive determination of Topiramate based on molecular imprinted polymer approach was produced by Khalifa et al. [31]. The linear concentration ranges and detection limits of the developed sensors were reported to be as following: 2.7×10^{-10} – 4.9×10^{-3} M, 5.0×10^{-11} M for voltammetric sensor (MIP/GO/GCE); 1.0×10^{-9} – 3.4×10^{-3} M, 2.4×10^{-10} M for potentiometric sensor (MIP/PVC/GCE). Electroanalytical topiramate sensors was applied in human serum samples, urine sample and pharmaceutical tablets.

El-Naby developed potentiometric sensor based on β–cyclodextrin:phosphomolybdic acid organic–inorganic hybrid material as a ionophore incorporating a plasticized PVC membrane with dioctyl phthalate (DOP) or *o*–nitrophenyloctyl ether (*o*–NPOE) for the determination of pregabalin in pharmaceutical formulations [32]. They showed that this sensor had a linear concentration range of 1.0×10^{-6} – 1.0×10^{-1} M, a detection limit of 6.0×10^{-7} M and response time of 5s.

The chemical structures of the mentioned anti–epileptic drugs are given in Fig. 1.

The linear concentration range, limit of detection, pH working range, response time and slope (mV/decade) of anti–epileptic drug sensors are summarized in Table 1. The gabapentin–selective sensor prepared by Abdallah and Ibrahim has the widest working range and the lowest detection limit [22]. The potentiometric valproate biosensor proposed by Özbek et al. has the widest pH working range [16]. The sensors prepared for the determination of lamotrigine and pregabalin have a very short response time of 5 s [28,32].

2. Conclusion

In this study, we reviewed potentiometric sensors which were developed for the determination of anti–epileptic drug molecules in biological and pharmaceutical preparations. While the determination of anti–epileptic drugs in pharmaceutical samples is important for content analysis and drug development, their determination in biological samples is very important in terms of drug metabolism, availability and toxicity. Potentiometric methods, which are easier to reach and cheaper than other analytical methods, can perform these analyzes quantitatively. Considering their working concentration ranges, response time, detection limit, selectivity and stability, it will be possible to analyze drug molecules in biological and pharmaceutical samples, which are otherwise not easy to perform with other analytical methods. Consequently, sensors prepared with potentiometry successfully detect drug molecules in various samples, and these methods will reach more application areas and more users in the coming years.

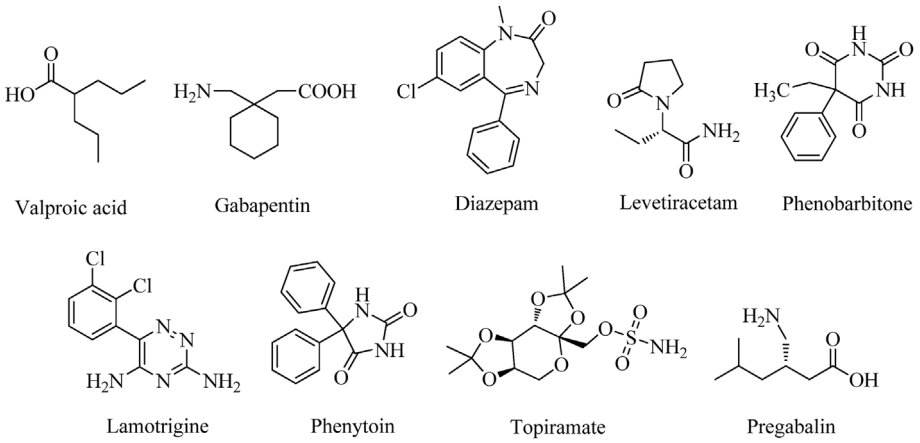

Fig. 1. The chemical structures of anti–epileptic drugs.

Table 1
Potentiometric performance characteristics of anti–epileptic sensors.

Anti-epileptic drug	Concentration range (M)	Limit of detection (M)	pH working range	Response time (s)	Slope (mV dec^{-1})	Ref.
Valproic acid	1.0×10^{-6} –1.0×10^{-1}	9.75×10^{-7}	4.0–11.0	<10	59.0 ± 3.6	[17]
Valproic acid	5.96×10^{-5} –1.0×10^{-2}	4.48×10^{-5}	3.0–7.0	5–10	−57.099	[18]
Valproic acid	4.0×10^{-5} –4.0×10^{-2}	1.0×10^{-5}	4.0–7.5	20	47.7	[19]
Valproic acid (PVC membrane)	9.9×10^{-6} –1.0×10^{-1}	5.0×10^{-6}	4.5–8.4	15	60.8 ± 0.9	[20]
Valproic acid (sol–gel membrane)	2.0×10^{-4} –1.0×10^{-1}	1.0×10^{-4}	3.5–7.5	10	60.3 ± 1.0	
Gabapentin	1.0×10^{-5} –5.0×10^{-2}	1.0×10^{-5}	1.8–3.2	10–35	59.8 ± 2	[21]
Gabapentin	1.0×10^{-10} –1.0×10^{-3}	4.8×10^{-11}	1.5–3.0	15	59.86	[22]
Diazepam			1.9–2.7	<30	67.6 ± 3.0	[23]
Diazepam	5.0×10^{-5} –1.0×10^{-2}	8.0×10^{-7}	3.0–5.0	5–10	58.6 ± 0.2	[24]
Levetiracetam	1.0×10^{-5} –1.0×10^{-1}	6.31×10^{-6}	6.0–8.0	25	24.0 ± 1.9	[25]
Phenobarbitone	5.0×10^{-6} –1.0×10^{-2}	3.50×10^{-6}	9.0–11.0	25–30	−59.1	[26]
Phenobarbitone	8.0×10^{-6} –1.0×10^{-2}	7.0×10^{-6}	9.0–11.0	25–30	−62.0	
Lamotrigine	1.0×10^{-6} –1.0×10^{-3}	8.0×10^{-7}	1.0–5.0	~30	30.8 ± 1.0	[27]
Lamotrigine	5.0×10^{-4} –9.0×10^{-3}	1.3×10^{-5}	4.6–5.8	5	57.14 ± 1.0	[28]
Phenytoin	1.0×10^{-5} –1.0×10^{-1}	6.0×10^{-6}	2.5–9.0	12–30	26.6	[29]
Phenytoin (I)	5.0×10^{-3} –5.0×10^{-6}	1.3×10^{-6}	6.0–10.0	≤35	30.9 ± 0.1	[30]
Phenytoin (II)	1.0×10^{-3} –1.0×10^{-6}	2.5×10^{-7}	6.0–10.0	≤30	28.9 ± 0.1	
Topiramate	1.0×10^{-9} – 3.4×10^{-3}	2.4×10^{-10}			−59.2 ± 0.4	[31]
Pregabalin	1.0×10^{-6} –1.0×10^{-1}	6.0×10^{-7}	1.5–3.7	5	59.6	[32]

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

[1] O. Özbek, M.B. Gürdere, A review on the synthesis and applications of molecules as anticonvulsant drug agent candidates, Med. Chem. Res. 29 (2020) 1553–1578, https://doi.org/10.1007/s00044-020-02595-4.
[2] O. Özbek, Ö. Isildak, The Use of valproic acid in the treatment of epilepsy and determination of biological matrices, Hacettepe Univ. J. Fac. Pharm. 42 (2022) 199–207, https://doi.org/10.52794/hujpharm.1062609.
[3] K.M. Matar, Quantification of levetiracetam in human plasma by liquid chromatography–tandem mass spectrometry: application to therapeutic drug monitoring, J. Pharm. Biomed. Anal. 48 (2008) 822–828, https://doi.org/10.1016/j.jpba.2008.05.035.
[4] O. Özbek, C. Berkel, Ö. Isildak, M.B. Gürdere, HPLC–based methods for the determination of levetiracetam in biological and pharmaceutical samples, J. Indian Chem. Soc. 99 (2022), 100348, https://doi.org/10.1016/j.jics.2022.100348.
[5] S.H. Han, Y.J. Kim, J.Y. Jeon, M.H. Hwang, Y.J. Im, J.A. Jeong, S.W. Chae, M.G. Kim, Rapid and sensitive analysis of valproic acid in human red blood cell by LC–MS/MS, Bull. Kor. Chem. Soc. 33 (2012) 1681–1685, https://doi.org/10.5012/bkcs.2012.33.5.1681.
[6] K.R. Ahmad, N. Rastkari, F. Kobarfard, K.O. Ahmad, A. Kebriaeizadeh, H. Pakdaman, An improved GC method for rapid analysis of valproic acid in human plasma without derivatization, Iran. J. Pharm. Res. (IJPR) 3 (2007) 37–42.
[7] T. Wattananat, W. Akarawut, Validated LC-MS-MS method for the determination of gabapentin in human plasma: application to a bioequivalence study, J. Chromatogr. Sci. 47 (2009) 868–871, https://doi.org/10.1093/chromsci/47.10.868.
[8] B. Purohit, P.R. Vernekar, N.P. Shetti, P. Chandra, Biosensor nanoengineering: design, operation, and implementation for biomolecular analysis, Sensors International 1 (2020), 100040, https://doi.org/10.1016/j.sintl.2020.100040.
[9] O. Özbek, Potentiometric PVC membrane ion–selective electrode for the determination of Sr(II) ions, Sensors International 3 (2022), 100185, https://doi.org/10.1016/j.sintl.2022.100185.
[10] O. Özbek, C. Berkel, Recent advances in potentiometric analysis: paper–based devices, Sensors International 3 (2022), 100189, https://doi.org/10.1016/j.sintl.2022.100189.
[11] Ö. Isildak, F.B. Egeli, O. Özbek, The use of different ionophores for the determination of Zn^{2+} ions, Sensors International 3 (2022), 100195, https://doi.org/10.1016/j.sintl.2022.100195.
[12] H.M. Abu Shawish, S.M. Saadeh, S.T. Al-kahlout, PVC membrane, coated-wire, and carbon-paste electrodes for potentiometric determination of vardenafil hydrochloride in tablet formulations and urine samples, Sensors International 3 (2022), 100175, https://doi.org/10.1016/j.sintl.2022.100175.
[13] S.M. Saadeh, H.M. Abu Shawish, M.Y. Abu Foul, Lowering detection limits of copper(II)-selective carbon paste electrodes using an SNO- and an SNNS- Schiff base ligands, Sensors International 3 (2022), 100151, https://doi.org/10.1016/j.sintl.2021.100151.
[14] Ö. Isildak, O. Özbek, Application of potentiometric sensors in real samples, Crit. Rev. Anal. Chem. 51 (2021) 218–231, https://doi.org/10.1080/10408347.2019.1711013.
[15] O. Özbek, C. Berkel, Ö. Isildak, I. Isildak, Potentiometric urea biosensors, Clin. Chim. Acta 524 (2022) 154–163, https://doi.org/10.1016/j.cca.2021.11.011.
[16] O. Özbek, A potentiometric sensor for the determination of potassium in different baby follow–on milk, water, juice and pharmaceutical samples, J. Food Compos. Anal. 115 (2022), 104937, https://doi.org/10.1016/j.jfca.2022.104937.
[17] O. Özbek, Ö. Isildak, I. Isildak, A potentiometric biosensor for the determination of valproic acid: human blood–based study of an anti–epileptic drug, Biochem. Eng. J. 176 (2021), 108181, https://doi.org/10.1016/j.bej.2021.108181.
[18] S.S. Soliman, G.A. Sedik, M.R. Elghobashy, H.E. Zaazaa, A.S. Saad, Greenness assessment profile of a QbD screen-printed sensor for real-time monitoring of

sodium valproate, Microchem. J. 182 (2022), 107859, https://doi.org/10.1016/j.microc.2022.107859.
[19] S. Sabah, M. Aghamohammadi, N. Alizadeh, Solid-State valproate ion selective sensor based on conducting polypyrrole films for determination of valproate in pharmaceutical preparations, Sensor. Actuator. B Chem. 114 (2006) 489–496, https://doi.org/10.1016/j.snb.2005.05.035.
[20] E.M.G. Santos, A.N. Araújo, Cristina M.C.M. Couto, M.B.S.M. Montenegro, Construction and evaluation of PVC and sol–gel sensor membranes based on Mn(III) TPP-Cl. Application to valproate determination in pharmaceutical preparations, Anal. Bioanal. Chem. 384 (2006) 867–875, https://doi.org/10.1007/s00216-005-0170-y.
[21] F. Jalali, E. Arkan, G. Bahrami, Preparation of a gabapentin potentiometric sensor and its application to pharmaceutical analysis, Sensor. Actuator. B Chem. 127 (2007) 304–309, https://doi.org/10.1016/j.snb.2007.07.019.
[22] N.A. Abdallah, H.F. Ibrahim, Potentiometric sensor of graphene oxide decorated with silver nanoparticles/molecularly imprinted polymer for determination of gabapentin, Carbon Lett 27 (2018) 50–63, https://doi.org/10.5714/CL.2018.27.050.
[23] C.G. Amorim, A.N. Araújo, M.C.B.S.M. Montenegro, V.L. Silva, Cyclodextrin-based potentiometric sensors for midazolam and diazepam, J. Pharm. Biomed. Anal. 48 (2008) 1064–1069, https://doi.org/10.1016/j.jpba.2008.08.012.
[24] N. Ghorbani, S. Hosseinzadeh, S. Pashaei1, A. Hosseinzadeh, Preparation of unique potentiometric carbon paste sensor for determination of diazepam in pharmaceutical applications, Int. J. Electrochem. Sci. 9 (2014) 7574–7586.
[25] O. Özbek, Ö. Isildak, Potentiometric PVC membrane sensor for the determination of anti-epileptic drug levetiracetam in pharmaceutical formulations, ChemistrySelect 7 (2022), e202103988, https://doi.org/10.1002/slct.202103988.
[26] H. Alrabiah, A. Al-Majed, M. Abounassif, G.A.E. Mostafa, Ionophore-based potentiometric PVC membrane sensors for determination of phenobarbitone in pharmaceutical formulations, Acta Pharm. 66 (2016) 503–514, https://doi.org/10.1515/acph-2016-0042.
[27] H.B. Sadeghi, S.A. Ebrahimi, A. Tamaddon, F. Bozorgvar, H. Afifinia, N. Almasian, S. Mollaei, Potentiometric sensing of lamotrigine based on molecularly imprinted polymers, Electroanalysis 23 (2011) 2716–2723, https://doi.org/10.1002/elan.201100140.
[28] N. Rajendraprasad, Novel membrane sensor for determination of lamotrigine in pharmaceuticals and urine, Curr. Chem. Lett. 8 (2019) 87–96, https://doi.org/10.5267/j.ccl.2019.002.002.
[29] Y.K. Al-Bayati, R.R. Karabat, Potentiometric study of phenytoin–PVC membrane electrodesfor determination of phenytoin in pharmaceutical preparations, Journal of Al-Nahrain University 18 (2015) 79–87.
[30] M. El-Tohamy, S. Razeq, M. El-Maamly, A. Shalaby, Construction of different types of ion-selective electrodes and validation of direct potentiometric determination of phenytoin sodium, Cent. Eur. J. Chem. 8 (2010) 937–945, https://doi.org/10.2478/s11532-010-0064-5.
[31] M.E. Khalifa, T.A. Ali, A.B. Abdallah, Molecularly imprinted polymer based GCE for ultra-sensitive voltammetric and potentiometric bio sensing of topiramate, Anal. Sci. 37 (2021) 955–962, https://doi.org/10.2116/analsci.20P313.
[32] E.H. El-Naby, Potentiometric sensing platform for selective determination of pregabalin in pharmaceutical formulations, J. Anal. Bioanal. Chem. 3 (2019) 49–56, https://doi.org/10.17352/ojabc.000011.