Diltiazem–tetraiodide bismuthate (III) based PVC membrane for selective determination of diltiazem hydrochloride

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Abstract;

A new coated-wire electrode based on PVC membrane plasticized with dioctyl phthalate (DOP) and containing the diltiazem-tetraiodido bismuthate (III) ion association coated on a silver wire was constructed and used for potentiometric determination of diltiazem hydrochloride. The electrode performance was characterized and optimized according to the following experimental criteria: membrane composition, soaking time, working pH range, and response time. The interference caused by different species was investigated as well. The best membrane composition was found to be 49.75% of PVC and DOP, 0.5% ion pair. This sensor showed a linear response with a good Nernstian slope of 57.60±1.38 mV/decade over the concentration range
$5.0\times10^{-5} – 2.50\times10^{-2}$ M, the detection limit was 2.88×10^{-5} M, and it was usable within a wide pH range of
2.5–8.0. The electrode showed a fast response time (18 sec), with a relative long lifetime (2.4 months, 2 h a day). The isothermal coefficient (dE°/dT) of the electrode was calculated and found to be 5.36×10^{-4} V/℃ within
20 – 80℃, which exhibits a good thermal stability. The coted-wire electrode was successfully applied for the potentiometric determination of diltiazem hydrochloride both in pure form and pharmaceutical preparations. The dissolution test of the drug was carried out as well.

Keywords Diltiazem hydrochloride, Ion-pairing agent, Nernstian response, Selectivity coefficient, Tetraiodido bismuthate (III)

Introduction

Ion-selective electrodes are electrochemical sensors that allow potentiometric measurements of the activity of particular species in aqueous or mixed solvents [1]. The introduction of ion-selective electrodes into pharmaceutical analysis has significantly contributed to the increase in the number of compounds that can be determined potentiometrically.

ISEs are usually classified by the membrane material into glass, crystalline, and polymeric electrodes. ISEs with polymeric membranes comprise the largest group of electrodes where poly (vinyl chloride) (PVC) is the most favored and widely used polymer [2]. The design of a conventional selective electrode usually consists of a membrane containing the ion of interest in the form of an ion-pair with an oppositely charged lipophilic ion. The membrane is interposed between a reference (internal) and the test (external) ion solutions, and the complete electrochemical cell comprises the membrane, as well as the internal and external reference electrodes [1]. A simple ISE design was built by Hirata and Date [3] where impregnated silicone rubber membrane was deposited on a metal wire and the internal electrode and solution were eliminated. Later, this sort of construction was called the coated-wire electrodes (CWEs), that refer to a type of ion-selective electrode in which an electroactive species is incorporated in a thin polymeric film coated directly to a metallic conductor [4].

Diltiazem is a benzothiazepine calcium-channel blocker and class IV antiarrhythmic. It is a peripheral and coronary vasodilator with limited negative inotropic [5]. Several analytical methods for the determination of diltiazem hydrochloride (DLT) have been reported in the literature using high performance liquid chromatography [6–12], spectrophotometry [13–15], and voltammetry [16, 17]. A plastic selective PVC membrane based on diltiazem-tetraphenylborate ion-associate has been used for potentiometric determination of diltiazem HCl as well [18].

The ISEs technique in comparison to the aforementioned analytical methods is more preferable in relating to the simplicity, low-cost instrumentation system, low consumption of time and hazardous organic solvents, in addition to the high selectivity with good accuracy and precision. In this work, we have used the negatively charged coordinate complex tetraiodido bismuthate (III) (TIB) to form DLT-TIB ion-pair which was incorporated into a PVC coating matrix to construct a new coated-wire sensor for the potentiometric determination of diltiazem hydrochloride.
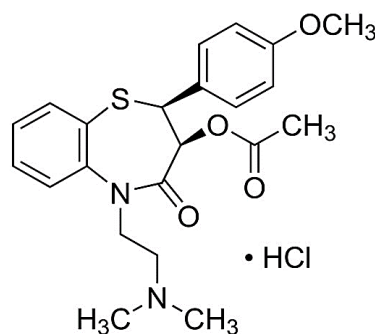
Figure 1. Chemical structure of DLT

Experimental

Materials

Diltiazem hydrochloride was purchased from *Chemica Drugs company LTD* (India). Bismuth nitrate, potassium iodide, and all chemicals and excipients were of analytical or pharmaceutical grade. Bi–distilled water was used to prepare all aqueous solutions. Tetrahydrofuran (THF) was from Riedel–de Haën, dioctyl phthalate (DOP) from Merck, and PVC of relatively high molecular weight was from Fluka.

Apparatus

A digital Multimeter (UNI–T, China) with an accuracy of ±0.1 mV was used to record the potentiometric measurements. pH meter (Sartorious, Germany). Electronic balance with an accuracy of ±0.1 mg (Sartorious, Germany). Ultrasonic waves apparatus (Wisd, Korea). HPLC instrument with an autosampler (Agilent 1200, USA). UV spectrophotometer (Shimadzu 1800, Japan). Dissolution tester (Electrolab TDT08L, India), Magnetic stirrer with hotplate (Wisd, Korea).

Solutions

A stock solution of diltiazem hydrochloride (0.1M) was prepared by dissolving an appropriate amount of the drug in water and then sonicated to aid in dissolution. Aliquots of stock solution were transferred into suitable volumetric flasks and diluted to volume with water to obtain a series of solutions within the concentration range of (0.7×10^{-1} – 5.0×10^{-6} M).

Ten tablets or capsules contents were accurately weighed and finely powdered in a mortar; the required amount from the tablet or capsule powder was dissolved in about 70 mL of water and transferred to a 100 mL volumetric flask, then completed to volume with water and sonicated for about 10 minutes. The resulting solution was filtered and subjected to potentiometric measurements for assay determination of diltiazem hydrochloride in its pharmaceutical preparations.

Preparation of the electroactive substance

A 25 mL of the coordinate complex $[BiI_4]^-$ (0.05M), was first prepared in an acidic medium HCl 2 M by adding 5.50 mmol (10% excess) of KI solution to 1.25 mmol of $Bi(NO_3)_3$ solution. Then, the electroactive material DLT–TIB was prepared from an acidic aqueous medium by adding the coordinate complex solution to 2.50 mmol of diltiazem hydrochloride solution (50 mL, 0.05 M) dissolved in HCl 1 M to yield a deep yellowish orange precipitate, which was filtered off, washed thoroughly with distilled water, and finally dried at room temperature. The predicted composition of the resulted ion–pair compound has a molar ratio of 1:2 and the suggested formula is $DLT_2[BiI_4]$.

Construction of the CWE electrode

A polymeric matrix solution containing equal weights of PVC and DOP dissolved in tetrahydrofuran (THF) solvent was first prepared. Then it was mixed with the ion–pair compound (IP) dissolved in THF. The solvent was allowed to evaporate until a thick coating solution is obtained.

The coated wire was prepared as described in Reference [4]. The exposed Ag wire was firstly washed with suitable detergent and water, then it was dried with acetone, and finally rinsed with chloroform and allowed to dry. The Ag wire was placed vertically to achieve a uniform coating. The wire was coated by quickly dipping about 2 cm of the exposed Ag wire into the coating solution several times and then the film of PVC solution was left on the wire to dry in air for about 1 min. The dipping and drying procedure is repeated until a plastic bead, with an

approximate diameter of 2 mm, is obtained. The coated membrane was allowed to dry in air for a few hours, then the coated wire was installed in the electrode's body which in turn was in conjunction with an external Ag/AgCl reference electrode that is immersed into KCl 1 M electrolyte. The constructed CWE electrode is represented as follows:

Ag | Membrane | Test solution (DLT, xM) | KCl 1 M solution | AgCl, Ag

Selectivity of the electrode

The effect of some interfering substances including inorganic ions, and pharmaceutical excipients on the measured emf of the cell was examined. The ability of an ion-selective electrode to distinguish a particular ion from other is quantitively expressed by means of the selectivity coefficient. The matched potential method (MPM) that has been advocated by IUPAC in a technical report [19] to calculate the selectivity coefficients K_{AB}^{Pot} was applied. In this method, a specific amount of primary ion ($\grave{a}_A$) is added to a reference solution (a_A) and the membrane potential change is measured. In a separate experiment, the ISE is placed back into an identical reference solution and interfering ions (a_B) are successively added until the same potential change is registered. The selectivity coefficient is then calculated as the ratio of the primary ion and interfering ion activity increases resulting in the same potential change [2, 20]:

$$K_{AB}^{Pot} = \frac{a_A - \grave{a}_A}{a_B}$$

Results and Discussion

Conditioning the electrode

The freshly prepared electrodes usually require pre-conditioning before use. This process usually involves soaking the membrane into a solution of the ion to be sensed, followed by repeated measurements at various concentrations of the test ion, until the response is rapid and reproducible [21]. The electrode after removing from the conditioning solution, should be rinsed and soaked for 10 – 20 min in deionized water before the actual measurements [4].

The prepared sensor was soaked into a solution of 0.01M diltiazem hydrochloride and the calibration curves were plotted at different time intervals. The electrode required very short conditioning time and gave a good Nernstian response 1 hour after soaking within the concentration range of $5.0{\times}10^{-5} – 2.5{\times}10^{-2}$ M.

Membrane composition

Different compositions of coating solution to prepare the coated wire membranes were studied. These membranes have variant percentages of ion–pair substance (0.25 – 1.0 %) and equal amounts of PVC and DOP. The calibration curve of E, mV vs. the negative logarithm of DLT concentration (pC_{DLT}) of each composition was constructed. The response characteristics including slope, linear range, limit of detection, and correlation coefficient were directly determined from the corresponding calibration curve and are given in Table 1. The optimum composition was accomplished with the electrode No. 3, which showed the best Nernstian response with a slope of 57.60±1.38 mV/decade, where it was chosen for further study. When IP ratio is higher than 1% by mass, the slope value considerably decreased.

Table 1. Composition and analytical characteristics of the prepared electrodes

No.	Coated membrane %		Slope, mV/decade	R^2	Linear range, M	LOD, M
	PVC and DOP	IP				
1	49.88	0.25	55.23	0.9991	$5.0{\times}10^{-5} – 2.5{\times}10^{-2}$	$3.48{\times}10^{-5}$
2	49.82	0.37	56.29	0.9992	$5.0{\times}10^{-5} – 2.5{\times}10^{-2}$	$3.11{\times}10^{-5}$
3	49.75	0.50	57.60	0.9994	$5.0{\times}10^{-5} – 2.5{\times}10^{-2}$	$2.88{\times}10^{-5}$
4	49.69	0.63	55.18	0.9990	$5.0{\times}10^{-5} – 2.5{\times}10^{-2}$	$3.23{\times}10^{-5}$
5	49.63	0.75	52.39	0.9984	$7.5{\times}10^{-5} – 1.0{\times}10^{-2}$	$6.50{\times}10^{-5}$
6	49.50	1.00	48.47	0.9984	$7.5{\times}10^{-5} – 1.0{\times}10^{-2}$	$6.58{\times}10^{-5}$

Effect of pH

The influence of pH of the test solution on the potential response was investigated. The pH value was adjusted by the addition of small volumes of concentrated solutions of HCl or NaOH. The emf readings against the pH–values within the concentration range of $5.0 \times 10^{-4} – 5.0 \times 10^{-3}$ M, were plotted, Fig. 2. The potential measurements were practically pH independent over a wide pH range of 2.50 – 8.0 and therefore the sensor can be safely used for determination of diltiazem hydrochloride within the suggested working pH range. The CWE response is usually affected by the interference from hydrogen ions at low pH values, while the hydroxide ions are contributed to the interference at pH > 8.0.
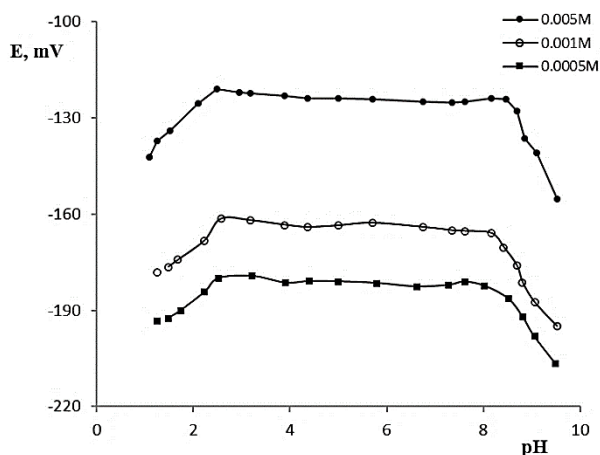

Figure 2. The working pH range of the electrode

Lifetime of CWE

The response slope does not change significantly with time, although a fall in slope is a strong indication that the electrode is nearing the end of its useful life [22]. The loss of plasticizer, carrier, or ionic site from the polymeric film due to leaching into the sample usually leads to a slow decrease in slope over the carrier–based sensors lifetime [2, 20].

The usable lifetime of the prepared electrode was estimated by continuous soaking of the membrane into an aqueous solution of 0.01M diltiazem hydrochloride at room temperature, then the calibration graphs of E, mV vs. pC_{DLT} at various time intervals were plotted. This sensor has an operational lifetime of at least 6 days (2.4 months, 2 h/day) with decrease in slope not more than 10%.

Response time

One important characteristic of an analytical sensor is its response time. The response time of ISE is the time required to achieve a steady emf response within ± 1 mV of the equilibrium value after transferring from one solution to another [22]. Therefore, the practical response time of the fabricated electrode was recorded for different concentrations of DLT solution within 1.0×10^{-4} to 1.0×10^{-2} M starting from the lower to the higher concentration. The potential readings vs. time plot for the response of the sensor, is shown in Fig. 3, where the equilibrium potential was achieved in approximately 18 ± 2 sec.
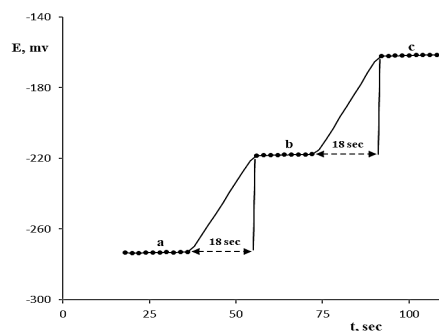

Figure 3. Potential–time curve for response time of DLT electrode

Temperature Effect

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The effect of temperature on the electrode response was studied. The calibration curves of E, mV vs. pC_{DLT} at different temperatures of the test solution ranging from 20℃ to 80℃, were plotted. The slopes and standard electrode potentials E° were directly determined from the calibration curve where E° was obtained as intercept when pC_{drug} = 0, Table 2. By applying Antropov's equation [23], E° values at different temperatures were plotted vs. (t–25), where t is the temperature of the test solution. The slope of E° vs. (t–25) plot represents the isothermal coefficient dE°/dT of the sensor, which was equal to 0.539 mV/℃ amounting to 5.39×10^{-4} V/℃ within the studied temperature range. This small value reveals a good thermal stability of the electrode. High temperature (usually > 60℃) cause significant decrease in slope of the conventional PVC ISE because the deterioration of the membrane, however the coated–wire type showed better thermal resistance at elevated temperatures with no considerable change in the response characteristics.

Table 2. Response characteristics at different temperatures

Temperature (℃)	Slope (mV/decade)	E° (mV)
20	56.87	166.58
30	57.09	172.20
40	57.27	178.39
50	57.16	182.02
60	57.30	188.22
70	57.62	193.02
80	55.79	199.75

Effect of interfering ions

The measured selectivity coefficients of the sensor are presented in Table 3, where the small values reflect the high selectivity of the electrode response toward diltiazem cation DLT^+ in presence of common inorganic ions, in particular the ones that may form coordinate complexes with the electroactive material's components. The sugars, which are usually formulated in pharmaceutical preparations do not interfere as well.

Table 3. Potentiometric selectivity coefficients determined by MPM method

Interferent	$K^{pot}_{CLP, j^{\pm}}$ *	Interferent	$K^{pot}_{CLP, j^{\pm}}$
K^+	2.76×10^{-3}	Ni^{2+}	3.83×10^{-4}
Na^+	3.00×10^{-3}	Co^{2+}	2.02×10^{-4}
NH_4^+	6.92×10^{-4}	Zn^{2+}	1.42×10^{-4}
Ca^{2+}	4.52×10^{-4}	Fe^{3+}	1.13×10^{-3}
Mg^{2+}	3.41×10^{-4}	SCN^-	2.76×10^{-3}
Pb^{2+}	1.91×10^{-3}	Lactose	2.59×10^{-4}
Hg^{2+}	1.42×10^{-3}	Mannitol	2.00×10^{-4}
Cu^{2+}	1.78×10^{-4}	Sucrose	1.65×10^{-4}

* $j^{\pm}$ represents the interfering ion

Electrode characteristics

Under the aforementioned experimental parameters, we have summarized the response and performance characteristics of the prepared CWE sensor in Table 4, while the potential curve vs. pC_{DLT} of the optimal membrane electrode is shown in Fig. 5.

Table 4. Response and operating characteristics of Diltiazem HCl CWE

Parameter	DLT–TIB CWE

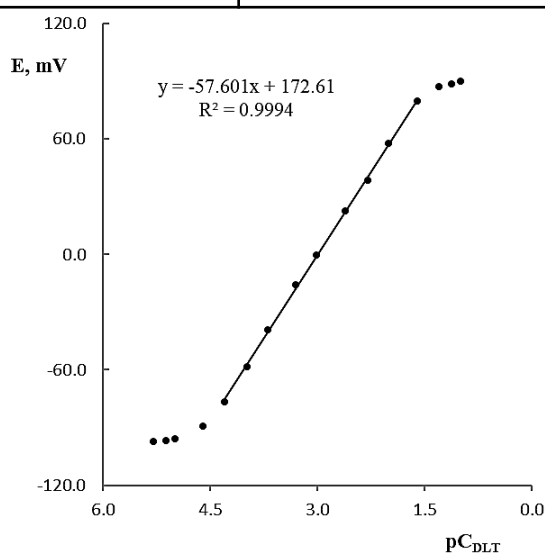| Composition, % w/w	Ion Pair 0.50, PVC and DOP 49.75
Slope, mV/decade	57.60 ± 1.38
R^2	0.9994
Linear range, M	$5.0 \times 10^{-5} - 2.50 \times 10^{-2}$
Detection Limit, M	2.88×10^{-5}
Working range, M	$2.88 \times 10^{-5} - 3.06 \times 10^{-2}$
Conditioning time, hour	1
Response time, sec	18 ± 2
Working pH range	$2.50 - 8.0$
Lifetime, months	2.4 (2h / day)

y = -57.601x + 172.61
R^2 = 0.9994

Figure 5. Potentiometric response curve for optimum electrode

Analytical application

Determination of diltiazem hydrochloride in pure and pharmaceutical forms

The new fabricated coated–wire electrode has been used successfully for potentiometric determination of diltiazem hydrochloride in pure form and in its pharmaceutical preparations. The calibration curve method was applied, where the emf values against pC_{DLT} graphs within the linear concentration range were plotted. The mean recoveries as well the relative standard deviations that are given in Table 5, were calculated after five replicates. The percentage recoveries ranged from 97.67 to 101.66% and RSDs were (0.97–3.07%), where the obtained results confirm the good accuracy and precision of the proposed method.

Different dosage forms and strengths of diltiazem hydrochloride available on the local market (Barakat Pharma); Adizem 60 mg (delayed release tablets), and Adizem 90, 120, 180 mg (sustained–release capsules), were analyzed. The mean results of drug content, and the corresponding recoveries and relative standard deviations of five replicates for each sample are shown in Table 6. Student's t – and F–tests (at 95% confidence limit) [24] were applied to check the validity of the proposed method. The calculated t – and F–values did not exceed the tabulated values at the corresponding degrees of freedom as shown in the table, while the assay results (the percentage of labeled amount) were in good agreement with those obtained by applying the official HPLC method.

Table 5. Statistical and analytical results for determination of diltiazem hydrochloride in pure solutions

C_{taken}	$C_{found} \pm SD$, mg/L	Recovery %	RSD%

M	mg/L			
5.0×10^{-5}	22.55	22.02 ± 0.68	97.67	3.07
1.0×10^{-4}	45.10	44.69 ± 0.80	99.09	1.79
5.0×10^{-4}	225.50	226.58 ± 0.68	100.48	1.02
1.0×10^{-3}	451.00	454.52 ±12.87	100.78	2.83
5.0×10^{-3}	2255.00	2246.81 ± 56.92	99.64	2.53
1.0×10^{-2}	4510.00	4584.96 ± 86.52	101.66	1.89
2.5×10^{-2}	11275.00	11103.64 ± 108.03	98.48	0.97

Table 6. Assay results for determination of diltiazem hydrochloride in tablets and capsules

Sample	Method	$\overline{\text{X}}$ ± SD (mg/Tab)	Assay %	RSD %	t–value [a]	F–value [b]
Adizem 60	CWE electrode	60.80 ± 0.69	101.34	1.14	2.46	7.67
	HPLC	59.96 ± 0.25	99.93	0.42 [c]		
Adizem 90	CWE electrode	95.98 ± 1.28	106.65	1.34	2.33	12.74
	HPLC	94.56 ± 0.36	105.07	0.38 [c]		
Adizem 120	CWE electrode	121.11 ± 1.59	100.92	1.32	1.72	12.53
	HPLC	122.41 ± 0.45	102.01	0.37 [c]		
Adizem 180	CWE electrode	190.57 ± 2.06	105.87	1.08	2.12	12.19
	HPLC	188.49 ± 0.59	104.72	0.31 [c]		

[a] Tabulated t–value is – 2.57.

[b] Tabulated one–tailed F–value (4, 2) is 19.25.

[c] Average of three determinations.

Dissolution Test

The dissolution rate of diltiazem hydrochloride from its dosage forms has been performed as directed in the U.S. pharmacopoeia [25]. One tablet or capsule was placed in each dissolution vessel containing 900 mL of water, while the temperature was maintained at 37.0 ± 0.5°C. The apparatus of type 2 (paddle) was rotating at 75 rpm (for Adizem 60 tablets) and 100 rpm (for Adizem 90, 120, 180 mg capsules). The potentiometric measurements were recorded using the proposed electrode and the amount of diltiazem hydrochloride dissolved in the medium at different time intervals were determined from the calibration curve. The results are shown in Table 7 and Table 8, and compared to the spectrophotometric method presented in the pharmacopeia where appropriate volumes from the dissolution medium were withdrawn, filtered, and diluted with water to a concentration that is similar of that of the standard solution (0.01 mg/mL) and the absorbances were measured at 237 nm. Six tablets or capsules of each batch were used to calculate the average percentages of the labeled amount of released diltiazem hydrochloride at the times specified where the results complied with the acceptance limits shown in Table (7) and (8).

Table 7. The dissolution results of Adizem 60 mg tablets

Time	Amount dissolved %		Acceptance criteria
	CWE electrode	UV method	
30 min	50.70	48.31	NMT 60 %
3 hours	97.27	94.62	NLT 75 %

Table 8. The dissolution results of Adizem 90 mg, 120 mg, 180 mg capsules

Time (hour)	Amount dissolved %						Acceptance criteria
	Adizem 90 mg		Adizem 120 mg		Adizem 180 mg		
	CWE electrode	UV method	CWE electrode	UV method	CWE electrode	UV method	
3	17.43	18.66	18.31	16.39	22.61	21.02	10 – 25 %
9	66.59	65.97	68.19	66.43	70.63	69.11	45 – 85 %
12	79.05	80.66	80.92	79.61	81.77	80.23	NLT 70 %

Conclusion

The new constructed electrode of silver wire coated with plasticized PVC membrane containing the co-ordinate complex tetraiodido bismuthate (III) as an ion-pairing reagent has proven to be useful analytical tool for direct potentiometric determination of diltiazem hydrochloride in pure and pharmaceutical forms. This sensor exhibited high selectivity to the analyzed drug with good accuracy and precision. Good operating characteristics presented in Nernstian slope, linear range, fast response, and high stability within a wide range of temperatures, were achieved. These advantages make the proposed method very simple, valuable and economical for the routine analysis of diltiazem hydrochloride in the quality control laboratories in pharmaceutical industry. Although, the potentiometric methods have not been introduced into the Pharmacopoeias so far, the present sensor provided a reliable and effective device for the assay and dissolution testing of the drug where the obtained results were in good agreement with the U.S. pharmacopeia method.

Conflict of Interest

The authors have no conflicts of interest regarding this investigation.

References

1. K. Vytřas, The use of ion-selective electrodes in the determination of drug substances, Journal of Pharmaceutical & Biomedical Analysis, 7(7), 789-812, 1989. https://pubmed.ncbi.nlm.nih.gov/2490089/.

   DOI: 10.1016/0731-7085(89)80001-9.

2. K. N. Mikhelson, Ion-selective electrodes, Springer Heidelberg, New York, 2013.

3. H. Hirata, K. Date, Copper(I) sulphide-impregnated silicone rubber membranes as selective electrodes for copper(II) ions, Talanta, 17, 883-887, 1970. https://doi.org/10.1016/0039-9140(70)80185-0.

4. H. Freiser, Ion-selective electrodes in analytical chemistry, vol 2, Plenum Press, New York, 1980.

5. A. Brayfield, Martindale: The complete Drug Reference, 38th ed, Pharmaceutical Press, 2014.

6. N. Sultana, M.S. Arayne, N. Shafi, A. Naz, S. Naz, and H. Shamshad, A RP-HPLC method for the simultaneous determination of diltiazem and quinolones in bulk, formulations and human serum, Journal of the Chilean Chemical Society, 54(4), 358–362, 2009. http://dx.doi.org/10.4067/S0717-97072009000400007.

7. N. Shafi, F.A. Siddiqui, N. Sultana, and M.S. Arayne, Concurrent determination of diltiazem, lisinopril, captopril, and enalapril in dosage formulations and in human serum by liquid chromatographic technique, Journal of Liquid Chromatography & Related Technologies, 38(15), 1466–1473, 2015.

   https://doi.org/10.1080/10826076.2015.1050503.

8. V.A. Chatpalliwar, P.K. Porwal, and N. Upmanyu, Validated gradient stability indicating HPLC method for determining diltiazem hydrochloride and related substances in bulk drug and novel tablet formulation, Journal of Pharmaceutical Analysis, 2(3), 226–237, 2012. https://pubmed.ncbi.nlm.nih.gov/29403747/.

   DOI: 10.1016/j.jpha.2012.01.003.

9. M. Arafat, Simple HPLC validated method for the determination of diltiazem hydrochloride in human plasma, International journal of pharmacy and pharmaceutical sciences, 6(9), 213-216, 2014.

   https://innovareacademics.in/journals/index.php/ijpps/article/view/1551.

10. K. H. Abu-Shandi, HPLC method development for the simultaneous determination and validation of diltiazem hydrochloride and its major metabolite desacetyl diltiazem hydrochloride, Der Pharma Chemica, 6(6), 358-365, 2014.

11. B. Kumar, B. Rajkamal, and B. Chandramowli, A validated RP-HPLC method for the determination of diltiazem in raw material and pharmaceutical dosage form, International Journal of Pharmaceutical Sciences and Drug Research, 10(6), 487-491, 2018.

     https://www.ijpsdr.com/index.php/ijpsdr/article/view/12.

12. M. A. Souza, C. Pereira, and G. A. Pianetti, Development and validation of a stability indicating HPLC method to determine diltiazem hydrochloride in tablets and compounded capsules, Brazilian Journal of Pharmaceutical Sciences, 53(3), 2017. https://doi.org/10.1590/s2175-97902017000300041.

13. M. A. Omar, O. H. Abdelmageed, A.A. Aldelgaber, and S. F. Saleh, Spectrophotometric determination of some calcium channel blockers using sulfochlorophenol-S, bromopyrogallol red, eriochromecyanine-R and pyrocatechoil violet, Natural Science, 5(4), 514-525, 2013.

     https://www.scirp.org/journal/paperinformation.aspx?paperid=30270.

14. R. Shrivastava, Spectrophotometric determination of diltiazem in pharmaceutical and in-vivo samples with Pd(II), International Journal of Pharmaceutical Sciences and Research, 4(12), 4676-4681, 2013. http://dx.doi.org/10.13040/IJPSR.0975-8232.4(12).4676-81.

15. G. Sandip, J. Santosh, S. Geeta, and T. Ashpak. Zero order and area under curve spectrophotometric methods for determination of diltiazem hydrochloride in pharmaceutical formulation, Indo American Journal of Pharmaceutical Research, 5, 1265-1270, 2015.

16. C. A. R. Salamanca-Neto, M. L. Felsner, A. Galli, and E. R. Sartori, In-house validation of a totally aqueous voltammetric method for determination of diltiazem hydrochloride, Journal of Electroanalytical Chemistry, 837, 159-166, 2019. https://www.x-mol.net/paper/article/5411927.

     DOI: 10.1016/j.jelechem.2019.02.026.

17. C. A. R. Salamanca-Neto, J. Scremin, J. T. Moraes, and E. R. Sartori, Voltammetric determination of diltiazem employing diamond electrode, XXI Brazilian Symposium of Electrochemistry and Electroanalysis, 2017.

18. M. R. Ganjali, T. Razavi, R. Dinarvand, S. Riahi, and P. Norouzi, New diltiazem potentiometric membrane sensor stands on theoretical calculations as a useful device for diltiazem hydrochloride analysis in pharmaceutical formulation and urine, International Journal of Electrochemical Science, 3(11), 1543-1558, 2008.

19. Y. Umezawa, K. Umezawa, and H. Sato, Selectivity coefficients for ion-selective electrodes: recommended methods for reporting K_{AB}^{Pot} values, Pure & Applied Chemistry, 67(3), 507-518, 1995.

     http://dx.doi.org/10.1351/pac199567030507.

20. E. Bakker, P. Bühlmann, E. Pretsch, Carrier-based ion-selective electrodes and bulk optodes. 1. General characteristics, Chemical Reviews, 97(8), 3083-3132, 1997. https://doi.org/10.1021/cr940394a.

21. J. Koryta, K. Štulík, Ion-Selective electrodes, 2nd ed, Cambridge University Press, New York, 1983.

22. H. Freiser, Ion-Selective Electrodes in Analytical Chemistry, vol 1, Plenum Press, New York. 1978.

23. L. I. Antropov, Theoretical Electrochemistry, Mir Publisher, Moscow, 1972.

24. J. N. Miller, J. C. Miller, Statistics and Chemometrics for Analytical Chemistry, 5th ed, Pearson Education Ltd, Edinburg Gate, Harlow, 2005.

25. United States Pharmacopeia 43, 2020.