International Journal of Pharmaceutical and Clinical Research
www.pharmaceuticaljournal.in
Online ISSN: 2664-7605, Print ISSN: 2664-7591
Received: 02-06-2021; Accepted: 15-06-2021; Published: 29-06-2021
Volume 3, Issue 1, 2021, Page No. 26-32

Development and validation of quality-control determination for ciprofloxacin in appearance of ciprofloxacin degradation products using ciprofloxacin selective sensor

Amir Alhaj Sakur*, Hashem A Dabbeet, Imad Noureldin
Department of Analytical and Food Chemistry, Faculty of Pharmacy, Aleppo University, Syria

DOI: https://doi.org/10.33545/26647591.2021.v3.i1a.21

Abstract
A PVC thin layer ciprofloxacin selective-electrodes was put together on account of Ciprofloxacin (CFX) examination proposes. The active material is CFX-tetradphenyl borate (CFX-TPB). Character description with analytical characteristic were concluded. Membrane plasticized using dioctylphthalate DOP. The put-together sensor has private reference Ag/AgCl sensor. Also, sensor has external reference sensor. The sensor exhibits an intimate Nernst slop in case of CFX-TPB percentage inside membrane was 7%. The electrode presented a quick response reached 9±1 seconds for an age of 384 hours of work without considerable alter in electrode parameters. In a ranges 2-6 for pH. The method occupied validation concerning selectivity, precision, Recovery, linearity, and limit of detection (LOD). of Results analysis based on statistic for submitted and comparison way applying variance ratio and Students were put into practice and so gave no consequential distinction between the methods respecting precision and accuracy, correspondingly. The sensor has been used as a Quality-Control indicator for direct definition of CFX putting in consideration attendance of its degradation materials (Desfluoro compound, Ethylenediamine analogue, Descarboxy analogue, Chloro analogue) in Ciprofloxacin tabs. go together with RSD smaller than 2% which point out decent precision, and likewise in absolute solutions against median recovery 99.99%, and a median RSD of 0.04% in case of 1 m.Mol.

Keywords: novel drug selective membrane, PVC membrane, ciprofloxacin, potentiometric determination, quality control, degradation products

Introduction

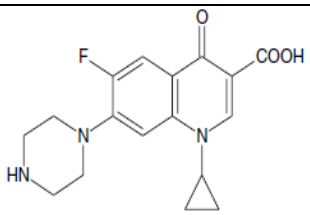
Ciprofloxacin. HCL (CFX) (Fig. 1) which considered as synthetic 2nd generation fluoroquinolone, and broad spectrum bactericidal wide employed in the handling of pertaining to respiration infections and urinary tract contamination by germs or diseases, osteomyelitis, gonorrhea, infections of the joints, infections of bones, and gastro-intestinal system infections caused by susceptible organisms. Demonstrating superior antimicrobial activity to that of Nalidixic acid and Norfloxacin against all pathogens tested. Ciprofloxacin Exerts its bactericidal effect by obstructing the bacterial DNA gyrase, which cause inhibiting of the DNA synthesis and preventing the growth of bacterial cells [1, 2, 3].

Many analytical technique reported for determination belonging to CFX.HCL including HPLC and RP-HPLC [4], UV spectrophotometry [5, 6 ,7 ,8 ,9], Derivative UV-Spectrophotometric [10, 11], Spectroflourimetric [12], Rayleigh light scattering [13], Capillary Zone Electrophoresis [14], Electrochemical Titrations [15], Electrical Micro-Titration [16], electrical potential procedure using CFX-selective electrodes [17], HPTLC procedure involving decisiveness and pureness examination of Ciprofloxacin drug in its tablets [18].

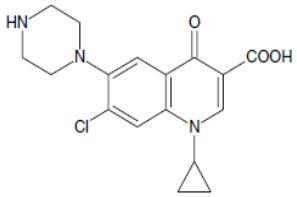
Stability considered as a predominant important criterion in quality control having a relationship to pharmaceutical dosage forms.

Breaking down CFX.HCL products or impurities showed in (Fig. 1) were reported as [19]:

- **Impurity B:** (Des-fluoro compound): no F ion on site 6.
- **Impurity C:** (Ethylenediamine analogue).
- **Impurity D**
- **Impurity E:** (Descarboxy analogue)
- **Chloro analogue**



Ciprofloxacin HCL



Impurity D

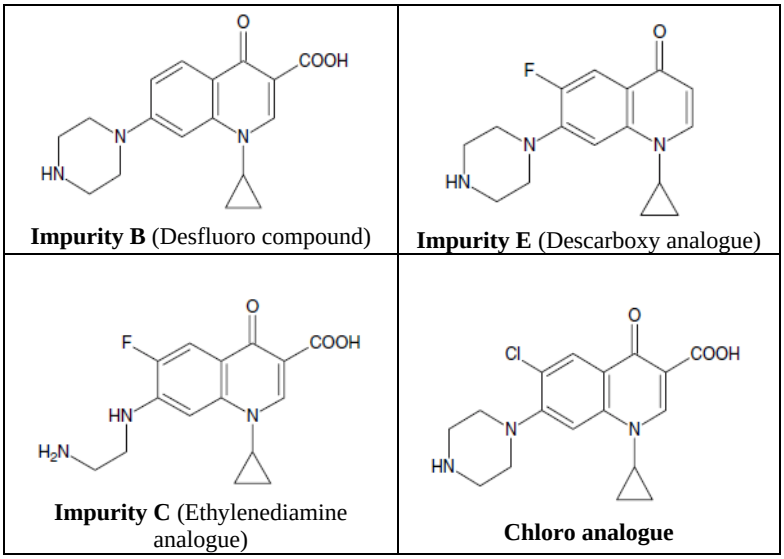


Fig 1: Structures of Ciprofloxacin.HCL and its impurities

Potentiometric method using ion-selective electrodes (ISEs) were proven to be a simple method to analysis CFX in its bulk solutions and pharmaceutical formulations, In previous works we found ISEs which uses PVC as a matrix for ion pair useful for the determination of a single drug providing fast result, simple analysis procedures, and over that offering high state of being selective towards the intended drug in the presence of inert substances in medications [20, 21, 22, 23, 24, 25], also we succeeded inventing a selective electrode for the concurrent determination of the two medications Ciprofloxacin and Metronidazole using a PVC membrane containing two ion pairs [26], beside Ciprofloxacin and Tinidazole polystyrene membrane also containing two ion pairs [27]. Finally reaching a novel electrode containing three different ion pairs of Ciprofloxacin, Metronidazole, and Minocycline which was found to be selective for the three drugs in their triad mixture [28]. Continuing to the study of how temperature variance affects the response of the ion selective electrode [29].

An attempt was made to investigate the sensitivity of the PVC-based CFX selective electrode toward Ciprofloxacin. HCL in the presence of its related compounds, also aimed at developing the technique as a quality control method providing assay of the active pharmaceutical ingredient CFX in the presence of its impurities already present or as a result of forced degradation studies in film-coated tablets.

Methods and used Materials

Devices

Electrochemical measures were taken with Radiometer pH/mV meter IONcheck-10, France, connected to CFX-tetraphenyl-borate salt (TPB)-polyvinyl chloride (PVC)-Dioctylphthalate (DOP) plasticized membrane electrical conductor working together with Ag/AgCl wire as an exterior reference electrode. GLP model 21/EU Crison pH-meter involved in pH adjustment. MS 300 Bante, China hot-plate magnetic stirrer with temperature probe was used to perform constant stirring and temperature adjustment. Weights taken using Sartorius analytical balance, Germany) preciseness ±0.1mg. Conductivity meter was used for the quality of the water used.

Reagents and Materials

Ciprofloxacin (CFX•HCl) 99.0% (Sigma-Aldrich), H Mw polyvinyl.CL (PVC) KSA, Na tetra-phenyl borate 99%, Dioctylphthalate (DOP) 99%, HCL, NaOH, KCL, THF (Merck, Germany). Bi-distilled water, silver wire (1 mm).

Caliber Drug Solutions

0.1 mol\L CFX•HCl (Mw=367.805 g\mol) Stock solution prepared by dissolving the correct weight of the CFX.HCl drug powder into 1 M KCL, this solution was stable for many weeks stored at darkness (4 °C). Serial dilution was accomplished to have practical solutions 1-10000 micro.mol. The last solutions found to be stable for only one week at 4°C. Britton buffer were used [30, 31].

Degradation products solutions preparation

Transferring 20 mg CFX.HCL powder to a 100-mL round glass bottle, then (HCL 2N) 20 mL is added. Heated in the dark at 80 ºC for 48 hours under refluxing. After we let the mixture to be cool again, we re-neutralized the solution using NaOH 2N. After evaporating till dryness with vacuum, the resulted remainder was taken out into volumetric flask (100mL) to have mother 0.2 mg/mL of CFX.Degradation solution [32, 33, 34].

Ion Selective Electrode

Ion Pairs preparing

The ion pair (IP) was arranged by mixing tantamount volumes of 10 mM CFX.HCL solution together with 20 mM tetraphenylborate Na (NaTPB) solution to form the ion pair (CFX-TPB). stirring for 30 minutes, then leaving for settling down. After filtering, we washed the precipitate with distilled water. After that, the resulting was dried for a full day, then dried at 60 °C, and stored in the refrigerator, the complex CFX-TPB were one to one.

Molding of ISM

Selective membrane was made by dissipating the proper weights of poly vinyl chloride and (DOP) as a plasticiser, with CFX-TPB to get the CFX selective membrane.

We dispersed the previous composition with the smallest quantity of THF, in a glass plate, allowing THF evaporated over-night, to gain CFX selective membrane.

Gathering of CFX-SE Cell

CFX-SE cell was gathered by connecting CFX-SE in connection against Ag/AgCl outer reference electrode. The circuit was completed attaching CFX-SE cell and the external reference electrode with a mVolt-meter. And so we accomplished the following electro-chemical cell [35]:

SE$_{CFX\text{-}TPB}$: Ag/AgCl-KCl (1M) + CFX (1mM) || CFX–TPB–DOP–PVC membrane || Test solution-KCl (1M) || Ag/AgCl

Electrode Calibration

We immersed the previous CFX-SE cell with the Ag/AgCl reference electrode in a sample of standard solutions 1-10000 µM of CFX in 1 M KCL at constant degree of temperature. Plotting the calculated potential vs. -log of CFX concentration (pC_{CFX}) was made. Between measurements, we washed the cell using distilled water.

Selectivity of CFX-SE

We estimated coefficients selectivity $K^{pot}_{CFX,B}$ for CFX-SE with respect to many excipients and compound in agreement with the IUPAC indication of acceptance [36, 37]. The coefficient of selectivity is determined by combined solution method which is known as the activity proportional relation of original and interfering electrically charged particle which produce the identical potential ulter under the same situations, we used the operation:

$K_{CFX,B}=(a'_{CFX}-a_{CFX})/a_B$

Whereas:

a'_{CFX}: the activity of the initial ion solution added

a_{CFX}: the activity of the reference solution of initial ion.

Effect of pH

Using 0.01 mol\L and 0.001 mol\L CFX solutions, we studied the effect of pH on the response of CFX-SE in the range of pH 1-8. The reading of the potential referring various pH

The effect of pH on the potential response of the prepared electrode was studied using 0.01 and 0.001 M CFX solutions. The pH of this solutions was adjusted between 1.0-8.0 using suitable amounts of 0.1 M KOH or HCL solution. The potential readings corresponding to different pH appraise were plotted. Also we repeated the study using 0.005 M Britton buffer.

CFX Determination in Drug Products

The following drugs were analyzed using the studied electrode:

Ciproflex 500 (tabs., ALPHA pharmaceutical, Aleppo): Each tablet include 500 mg of CFX.

CEPROZ® 500 (tabs., ElSaad pharmaceuticals, Aleppo): Each tablet include 500 mg of CFX.

CEPROZ® 250 (tabs., ElSaad pharmaceuticals, Aleppo): Each tablet include 250 mg of CFX.

Ten tabs. were weighted then smashed to have a fine powder. A tablet median wight dissolved in (KCL, 1M) 50mL, then diluted to 100 mL (KCL, 1M), diluting 10 times again, we have the final concentration determined.

Results with Discussions

Effect of IP% on the Potential

We considered linear part of calibration graph as the analytical range of the potentiometric sensor (quantitative part) and found it to be 10-10000 µM. On other hand TMR (qualitative part: embracing straight line of graphs with the lower curved part of the calibration graph) were 5.62-31622 µM (Fig 2). In TMR the response of the electrode to changing concentration becomes gradually less as the concentration decreases. In order to measure Samples in this lower range we must take more closely-spaced calibration points are needed to get accuracy, E% for each m.Volt will be incrementally higher as the slope reduces on the calculated concentration.

We found that increasing IP% in CFX-SE membrane increases reaction of the sensor and steadfastness of readings together with increasing the slope of electrode regarding $E(mV)=f(Pc_{CFX})$ obtaining -59.40 mV/decade at CFX-TPB percentage of 6 with linear range 100-10000 µM, and -59.04 mV.decade^{-1} at 7% CFX-TPB with wider linear range 10-10000 µM, and so we select the percent of the ion pair CFX-TPB 7% as the optimum percent in ion selective membrane. At larger percentages of IP a downward slope, and narrower range were demonstrated (Fig. 3). These results were mentioned in Table1.

Table 1: equations information earned by liner equation

	CFX-TPB				
IP %	5	6	7	8	9
S, mV.decade^{-1}	-43.97	-59.40	**-59.04**	-57.10	-55.69
b, mV.decade^{-1}	211.17	277.03	280.84	271.30	267.14
R^{2} *	0.957	0.999	0.9996	0.9997	0.9906

* Correlation coefficient

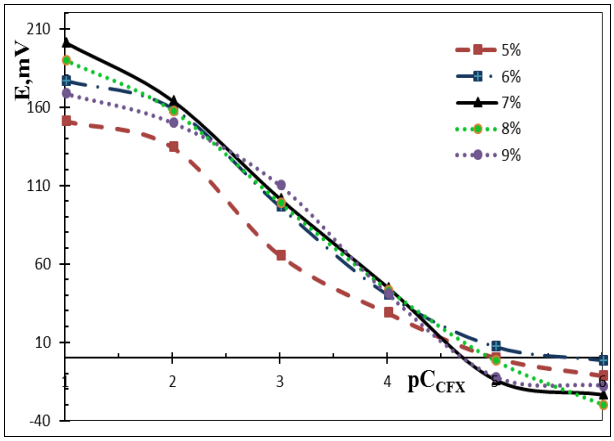


Fig 2: Effect of IP content on CFX calibration curves

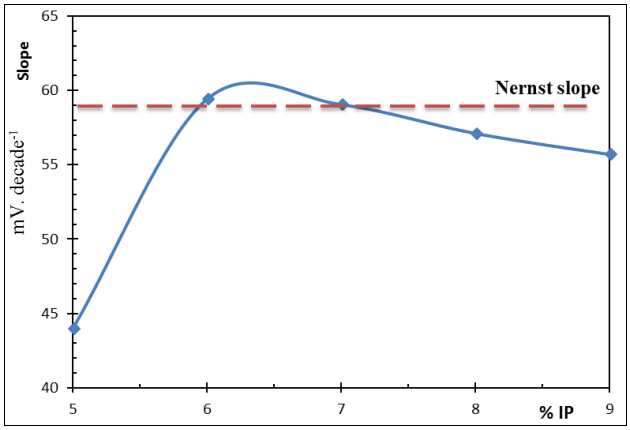


Fig 3: Effect of IP percentage in the ion selective membrane on the slope of the liner area for equation curve: E = f (P_{CCFX})

Electrode Selectivity

The acquire selectivity coefficients $K^{pot}_{CFX,B}$ for CFX-SE regarding many not organic interruptings, and few excipient are provided in table number 2. The outcome reveals a plausible selectivity for CFX in attendance of the following materials.

Table 2: Selectivity coefficient for considerably obstructing ions of proposed CFX-SE

Interfering, B	$K^{pot}_{CFX,B}$
Sodium chloride	6.3×10^{-3}
Potassium chloride	3.6×10^{-3}
Calcium chloride	7.1×10^{-3}
Magnesium chloride	3.8×10^{-3}
Magnesium stearate	5.1×10^{-3}
Microcrystalline Cellulose	2.9×10^{-3}
Glucose	2.8×10^{-3}
Starch	3.2×10^{-3}
Lactose monohydrate	1.9×10^{-3}

Effect of pH on response

We found that CFX-SE can work in pH ranging from 2.0 to 6.0, showing a constant potential in this wide range. And this range becomes wider when we use Robinson buffer (Fig. 4).

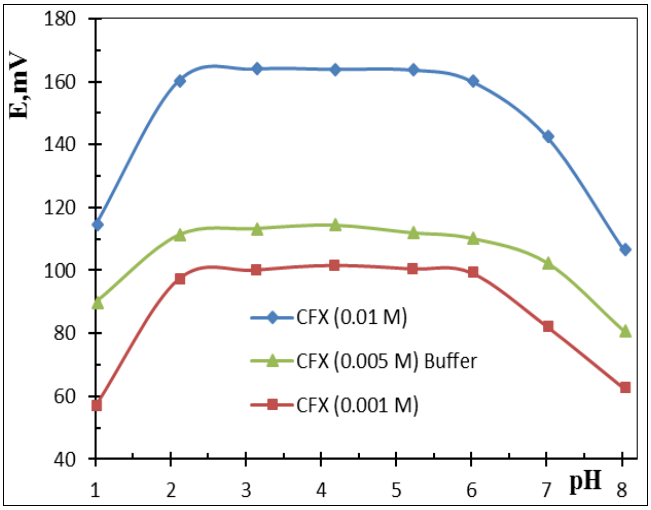


Fig 4: pH influence toward potential reaction for CFX-SE

When pH was decreased under 2.0, the potential measured with the electrode declined as a result of the decampment of hydrogen ions from the membrane of CFX-SE. Reaching pH values larger from 6.5 the potential also declined caused by the progressive enlarge of concentration of unprotonated CFX in the solution, or in consequence of IP ability to move within the CFX-SM [38, 39].

Lifetime Study

The lifetime of the electrode was appraise with assistance of curves of calibration, for that tests for CFX solutions (1–10000 µMol) were established from day to another with calculating of CFX-SE slope. The initially slope was - 59.04 mV\decade for CFX-TPB electrode near 25°C. While soaking the electrode in 1mM CFX solution for 20 days period, calibration plot slope declined delicately from the first day to 20th day reaching -53.12 mV.decade^{-1} after 16 days. This demonstrate the idea of the roinousing effect of immersion CFX-SE in liquid for an extended period of time.

Table 3: Response distinguishing for CFX-TPB sensor[a].

Parameter	CFX-TPB
IP%	7%
Slope, mV.decade^{-1}	-59.04 ± 0.11
Intercept, mV.decade^{-1}	280.84
Correlation coefficient (R^2)	0.9996
Linear range, µM	10-10000
TMR, µM	5.62-31622
LOD, µM	0.105
LOQ, µM	0.319
Response time for 1 mM, sec	9 ± 1
Life time, day	16
Working pH range	2.0-6.0* 2.0-6.5**

[a] 5 measurement
* No buffer
** Robinson buffer

Quantification of CFX

The examined sensor showed a good applicability in determination of CFX in its solutions and its formulations (Table 4). Also, specificity of the method was inspected by the way of appraising many mixtures composed of CFX and CFX breaking down results in many proportional relation inners the area of linearity, and good R% were established, as well as pertaining a minimum SD, and this results were as presented in (Table 5).

Table 4: CFX determinations in stock solutions with CFX-TPB sensor

Taken $C_{CFX\cdot HCl}$		CFX-TPB sensor *		
(µg/mL)	mol/L	R%	SD	RSD%
3.678	1×10^{-5}	99.62	0.0365	0.99
36.78	1×10^{-4}	99.56	0.4087	1.12
367.8	1×10^{-3}	99.99	0.1517	0.04
3678	1×10^{-2}	99.96	3.3615	0.09
*Average of five replicates				

Table 5: CFX determination with attendance of its degradation material in laboratory prepared mixtures using CFX Selective Sensor

Mixture No.	CFX (µg/mL)	Degradation Products (µg/mL)	Recovery CFX% Mean*
1	5.00	3.00	100.3
2	5.00	5.00	100.1
3	5.00	7.00	100.2
4	5.00	10.00	102.6
5	5.00	12.00	99.9
Mean ± SD	---	---	100.62 ± 0.12

*Average of three experiments

The CFX-TPB sensor showed a good applicability potentiometric usage in CFX determination inside the tablets of CFX, with comparing to the reference high-performance liquid chromatography [40]; the Average ± SD (R%) were 502.4 ± 0.89 mg (100.48%), 501.8 ± 1.30 mg (100.36%), and 251.8 ± 1.30 mg (100.72%) for Ciproflex, Ceproz 500, and Ceproz 250 respectively (Table 6).

Also we determined CFX inside three expired dosage forms was stored in our laboratory for approximately 10 years, using the developed CFX-TPB electrode; the $\bar{X}$ ± SD (R%) values for the expired products were 357.8 ± 1.30 mg (71.56%) for Ciproflex Expired since Jul-2010, 350.8 ± 1.30 mg (70.16%) for Ceproz 500 Expired since Sep-2009, and 163.18 ± 1.46 mg (65.27%) for Ceproz 250 Expired since Jun-2008 (Table 6).

Table 6: CFX Determinations within tablets applying suggested combined sensor

Commercial Name	Labelled CFX content (mg)	$\bar{X}$ ± SD, mg[a]	R%	t-value[b]	F-value[c]
Ciproflex	500	502.4 ± 0.89	100.48	1.5	1.1429
CEPROZ	500	501.8 ± 1.30	100.36	1.0289	2.4286
CEPROZ	250	251.8 ± 1.30	100.72	1.0289	1.3077
Expired products					
Ciproflex Expired since Jul-2010	500	357.8 ± 1.30	71.56	1.0289	2.4286
CEPROZ Expired since Sep-2009	500	350.8 ± 1.30	70.16	0.6859	2.4286
CEPROZ Expired since Jun-2008	250	163.18 ± 1.46	65.27	1.8355	5.7446

[a] 5 replicates Average.
[b] T-value at 95% trust level = 2.776.
[c] F-value at 95% trust level = 6.39.

Validation of Proposed Method

Linearity, LOD, and LOQ

Standard solutions of CFX 0.1-10000 µM (Pc_{Drug}=1-6) was measured 5 times using the suggested ISE with association of Ag/AgCl reference sensor. Averaged value of potentials was devised a plot vs Pc_{CFX} using equally balanced state: $E = S \times Pc_{CFX} + b$. The suggested sensor exhibited a linearity reaction from every direction ranging from 10-10000 µicro.mole in the 2-6 of pH. Detection limit of the methose (LOD) were 0.105µM, where quantification limit (LOQ) was 0.319µM, complement with IUPAC advice [39] (Table 3).

R% and Accuracy

We calculate R% of the proposed methods considering determined CFX to added known CFX. The intraday and inter day value informed with RSD%<2% reveal decent accuracy as in Table 4.

Deduction

We made a decision that CFX-TPB in Poly Vinyl Chloride membrane ion selective sensor propose a precious technical skill in favor of CFX-determination in its formulation and also in absolute samples in Presence of Ciprofloxacin degradation products and many impurities. The construction of sensor is something simple, fast, and can be remade. The sensor shows an excellent state of being selective regarding CFX in appearance of many inert substances in a medication, also the sensor has the advantage of using in the form of indicator in titrations of CFX and in CFX.HCL Quality-Control Determination notwithstanding demeanor of CFX breaking down Products.

An electro-active ion pair of CFX with TPB was carry out as sensor for the determination of CFX. The CFX-TPB membrane sensor showed good analytical performance, and exhibit a rapid, steady, with close to response of Nernest slop in a pertaining to comparison broad concentration of the CFX drug (from 10-10000 µicro.M.

The suggested sensor accomplished limit of detection (LOD) of 0.105 µM, and limit of quantification (LOQ) value of 0.319 µM, accompanied time for response 9±1 seconds. All suggested electrodes have a measurement pH ranges 2.0-6.0 without using any buffer.

The CFX determination directly gave intermediate R% 99.99, with RSD% 0.04% at 1 mM (367.8 µg/mL CFX). The acquire results were inner area of approval area (less than 2%) for exactness and larger than 99.56 % of R % on behalf of accuracy. CFX-SE was used as a tool which indicates CFX notwithstanding the Presence of Ciprofloxacin Degradation Products in its medicinal substance and likewise in absolute solutions.

References

1. Goodman and Gilman's. The pharmacological basis of therapeutics, 9th edn. McGraw-Hill, New York, 1996, 1065.
2. Johannsen EC, Sabatine MS. Pharm Cards: Review Cards for Medical Students, Fourth Edition (Wolters Kluwer, Lippincott Williams & Wilkins, 2010).
3. National Center for Biotechnology Information. Pub Chem Database. Ciprofloxacin hydrochloride, CID=62999, https://pubchem.ncbi.nlm.nih.gov/compound/Ciprofloxacin-hydrochloride (accessed on Nov. 24, 2019)
4. Kawas G, Marouf M, Mansour O, Sakur AA. Analytical

Methods of Ciprofloxacin and its Combinations Review, Research Journal of Pharmacy and Technology,2018:11(5):2139-2148.
5. Kazan R, Mandil H, Sakur AA. Determination of some Antibiotic of fluoroquinolone derivative In Pharmaceutical preparations using Spectrophotometric Analysis, 2009, M. Sc. Thesis, Fac. of sci., Aleppo University.
6. Cazedey ECL, Salgado HRN. Spectrophotometric Determination of Ciprofloxacin Hydrochloride in Ophthalmic Solution, Advances in Analytical Chemistry,2012:2(6):74-79.
7. Obaydo RH, Sakur AA. A Green Analytical method Using algorithm (PCCA) for extracting components contribution from severely overlapped Spectral Signals in pharmaceutical mixtures, Research Journal of Pharmacy and Technology,2019:12(9):4332-4338.
8. Obaydo RH, Sakur AA. Fingerprint Spectrophotometric Methods for the Determination of Co-Formulated Otic Solution of Ciprofloxacin and Fluocinolone Acetonide in Their Challengeable Ratio, Journal of Analytical Methods in Chemistryl, 2019, 14.
9. Obaydo RH, Sakur AA. Spectrophotometric strategies for the analysis of binary combinations with minor component based on isoabsorptive point's leveling effect: An application on ciprofloxacin and fluocinolone acetonide in their recently delivered co-formulation, Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy,2019:219:186-194.
10. Kharat R, Jadhav S, Tamboli D, Tamboli A. Estimation of Ciprofloxacin Hydrochloride in Bulk and Formulation by Derivative UV-Spectrophotometric Methods, International Journal of Advances in Scientific Research,2015:1(03):137-144.
11. Kazan R, Mandil H, Sakur AA. Spectrophotometric Determination of Ciprofloxacin in Pharmaceutical Formalations Using Bromocresol Green, R. J. of Aleppo Univ. Science Series,2008:62:143-160.
12. Kazan R, Mandil H, Sakur AA. Spectroflourimetric Determination of Ciprofloxacin and Norfloxacin, Arab Journal of pharmaceutical Sciences,2009:4:93-101.
13. Li X, Cao Q, Wang F. Determination of ciprofloxacin hydrochloride in pharmaceutical preparation and biological fluid by Rayleigh light scattering technique, Wuhan University Journal of Natural Sciences,2009:14(1):70-74.
14. Michalska. Determination of ciprofloxacin and its impurities by capillary zone electrophoresis, Journal of Chromatography A,2004:1051(1-2):267-272.
15. Mandil H, Sakur AA, Nasser B. Determination of Some Antibiotic (Ciprofloxacin, Norfloxacin and Gatifloxacin) in Pure Form and Pharmaceuticals Formulations Using Electrochemical Titrations, Ph. D. Thesis, Fac. of sci., Aleppo University, 2013.
16. Xu-ZhiZhang. Simple and cost-effective determination of ciprofloxacin hydrochloride by electrical micro-titration, Chinese Chemical Letters,2017:28(7):1406-1412.
17. Mandil H, Sakur AA, Nasser B. Potentiometric determination of gatifloxacin & ciprofloxacin in pharmaceutical formulations, International Journal of Pharmacy and Pharmaceutical Sciences,2012:4(4):537-542.
18. Novakovic J, Nesmerak K, Nova H, Filka K. An HPTLC method for the determination and the purity control of ciprofloxacin HCl in coated tablets, Journal of Pharmaceutical and Biomedical Analysis,2001:25:957-964.
19. Aksoy B, Küçükgüzel I, Rollas S. Development and validation of a stability-indicating HPLC method for determination of ciprofloxacin hydrochloride and its related compounds in film-coated tablets," Chromatographia,2007:66:S57-S63.
20. Sakur AA, Bassmajei S, Dabbeet HA. Novel Moxifloxacin Ion Selective Electrodes for Potentiometric Determination of Moxifloxacin in Pure Form and Pharmaceutical Formulations, International Journal of Academic Scientific Research,2015:3(4):66-75.
21. Haroun M, Nashed D, Sakur AA. New electrochemical methods for the determination of Prasugrel using drug selective membranes, International Journal of Academic Scientific Research,2017:5(3):30-36.
22. Mansour O, Nashed D, Sakur AA. Determination of Clopidogrelbisulphate using Drug Selective Membranes, Research Journal of Pharmacy and Technology,2018:11(5):2017-2021.
23. AA Sakur, D Nashed, M Haroun, I Noureldin. Determination of Prasugrel Hydrochloride in Bulk and Pharmaceutical Formulation Using New Ion Selective Electrodes, Research Journal of Pharmacy and Technology,2018:11(2):631-636.
24. Dabbeet HA, Sakur AA. Development of an Electrochemical Method for the Determination of a Compound Derivative from Fluoroquinolone, 2016, M. Sc. Thesis in Applied Analytical Chemistry, Faculty of Pharmacy, University of Aleppo.
25. Mandil H, Sakur AA, Nasser B. New ion selective electrode for potentiometric determination of gatifloxacin in pure form and pharmaceutical formulations, Int J Pharm Pharm Sci,2013:5(2):423-428.
26. Sakur AA, Dabbeet HA, Noureldin I. Novel Drug Selective Sensors for Simultaneous Potentiometric Determination of both Ciprofloxacin and Metronidazole in Pure form and Pharmaceutical Formulations, Research J Pharm and Tech,2019:12(7):3377-3384.
27. Sakur AA, Dabbeet HA, Noureldin I. Novel Drug Selective Polystyrene Membrane for Simultaneous Potentiometric Determination of Ciprofloxacin and Tinidazole in Pure Form and Pharmaceutical Formulation, Research J. Pharm. and Tech,2020:13(12):5963-5971.
28. Sakur AA, Dabbeet HA, Noureldin I. Simultaneous Potentiometric Determination of Ciprofloxacin-Metronidazole-Minocycline in Triad Combination Using Novel Drug Selective Sensor, J. Global Trends in Pharm. Sci,2020:11(3):8255-8271.
29. Sakur AA, Dabbeet HA, Noureldin I. Estimation of Temperature Effect on PVC-Based Ciprofloxacin Selective Electrode Response, Research J Pharm. and Tech,2021:14(1):136-142.
30. Britton HTS, Robinson RA. Universal buffer solutions

and the dissociation constant of veronal, Journal of the Chemical Society (Resumed), 1931, 1456-1462.
31. Ebihara A, Kawamoto S, Shibata N, Yamaguchi T, Suzuki F, Nakagawa T *et al*. Development of a modified Britton-Robinson buffer with improved linearity in the alkaline pH region, Biojournal of Science and Technology, 2016, 3.
32. El-Bagary RI, El-Zaher AA, Elkady EF, El-Hakim MM, Mandour AA. Stability Indicating HPLC Method for the Simultaneous Determination of Ciprofloxacin Hydrochloride and Metronidazole in the Presence of Ciprofloxacin Acid Degradation Product, Asian Journal of Biochemical and Pharmaceutical Research,2015:5(1):5-17.
33. Attia KAM, Nassar MWI, El-zeiny MB, Serag A. Stability-indicating methods for the analysis of ciprofloxacin in the presence of its acid induced degradation product : A comparative study, Spectrochim Acta A Mol Biomol Spectrosc,2016:15(159):219-222.
34. Singh BK, Parwate DV, Srivastava S, Shukla SK. High performance thin-layer chromatographic selective and stability indicating method for assay of ciprofloxacin in pharmaceuticals, Der Pharma Chem,2010:2(4):178-188.
35. Moody GJ, Nassory NS, Thomas JDR. Calcium ion-selective electrodes based on calcium bis [di (*p*-1,1,3,3-tetramethylibuthyl phenyl)- phosphate] sensor and trialkyl phosphate mediators, Analyst (London),1978:103(1):68-71.
36. Buck RP, Lindner E. Recommendations for nomenclature of ion-selective electrodes, Pure and Applied Chemistry: Analytical Chemistry Division,1194:66(12):2527-2536.
37. Umezawa Y, Bühlmann P, Umezawa K, Tohda K, Amemiya S. Potentiometric selectivity coefficients of ion-selective electrodes part I. inorganic cations (technical report). Pure and Applied Chemistry: Analytical Chemistry Division,2000:72(10):1851-2082.
38. Bassmajei MS. Determination of Some Pharmaceutical Compounds by New Plastic Membrane Ion-Selective Electrodes. Doctoral diss., University of Aleppo, Aleppo, Syria, 2005.
39. Mandil H, Sakur AA, NASSER B. New ion selective electrode for potentiometric determination of gatifloxacin in pure form and pharmaceutical formulations, Int. J Pharm Pharm Sci,2013:5(2):423-428.
40. Kawas G, Marouf M, Mansour O, Sakur AA. Analytical Methods of Ciprofloxacin and its Combinations Review, Research Journal of Pharmacy and Technology,2018:11(5):2139-2148.