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Validated potentiometric method for the determination of sulfacetamide sodium; application to its pharmaceutical formulations and spiked rabbit aqueous humor

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ABSTRACT

Specific, accurate and precise electrochemical method was developed and validated for the determination of sulfacetamide sodium in presence of its co-formulated drug (prednisolone acetate) and its pharmacopoeial impurities. The method was based on fabrication of membrane sensor. The characteristics of electrochemical response were estimated, and the proposed sensor displayed excellent characteristics for the determination of sulfacetamide sodium in bulk powder, laboratory prepared mixtures, dosage forms and in spiked biological fluid (Rabbit aqueous humor). The sensor was constructed through the use of tetradodecylammonium bromide (TDB) as an anion exchanger and 2-nitrophenyl octyl ether (NPOE) as a plasticizer in polyvinyl chloride (PVC) matrix. The performance characteristics, sensitivity and selectivity were evaluated according to IUPAC guidelines. Linearity was achieved over the concentration range of $1 \times 10^{-4.5}$–1×10^{-2} M with Nernstian slope of 51.086 mV/decade over the pH range of 5–7. The sensor showed a rapid response (10–15 s) and good stability (up to 4 weeks). The obtained results were statistically compared with the official methods and no significant difference was found regarding accuracy and precision.

1. Introduction

Sulfacetamide sodium (Fig. 1a) is sodium acetyl[(4-aminophenyl) sulfonyl]azanide [1]. It is a sulfonamide antibacterial agent used for the treatment of conjunctivitis and management of most ophthalmic infections. It has high efficacy for topical use so it is used also for the treatment of acne [2]. Prednisolone acetate (Fig. 1b) is 11β,17-dihydroxy-3,20-dioxopregna-1,4-dien-21-yl acetate [1]. It is one of glucocorticoids that formulated for topical use as anti-inflammatory agent [2]. Sulfacetamide sodium and prednisolone acetate are co-formulated for the treatment of blepharitis and conjunctivitis [3].

Different analytical techniques have been reported for the determination of sulfacetamide sodium in its pharmaceutical formulations, biological fluids and water samples. They include UV-visible spectrophotometry [4–7], liquid chromatography [8–10], capillary electrophoresis [11,12], voltammetry [13]. Nevertheless, most of these methods require sample pretreatment, time-consuming steps, using sophisticated instruments, high cost and being non-applicable for determination of drugs in turbid and colored solutions.

Reviewing the literature revealed that few ion selective electrodes have been reported for the determination of sulfacetamide sodium [14,15] using a precipitation-based technique. These sensors did not take into account the selective determination of sulfacetamide sodium in presence of its impurities or prednisolone acetate as a co-formulated drug. So, the aim in the present work is to develop a potentiometric electrode for precise, selective and sensitive determination of sulfacetamide sodium in its pure form, pharmaceutical formulations and in rabbit aqueous humor without prior separation and extraction steps.

A potentiometric study was developed via the use of TDB which is a quaternary ammonium salt often used to develop anion selective electrodes. It is characterized by having a high lipophilicity and four long alkyl chains as shown in (Fig. 2) which improve the electrode sensitivity [16]. The anionic exchanger was embedded in PVC matrix plasticized with NPOE (Fig. 3). It plasticizes the membrane and adjusts its permittivity and the mobility of the ion exchanger sites to facilitate the inclusion of organic molecules [17].

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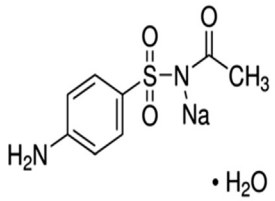

Fig (1a)

$C_8H_9N_2NaO_3S.\ H_2O$

Molecular weight: 254.24

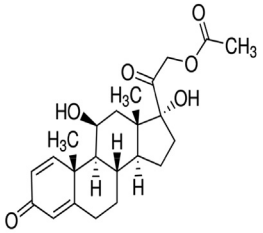

Fig (1b)

$C_{23}H_{30}O_6$

Molecular weight: 402.49

Fig. 1. Chemical structures of sulfacetamide sodium (1a) and prednisolone acetate (1b).

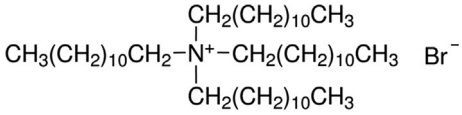

Fig. 2. The structure of tetradodecylammonium bromide (TDB).

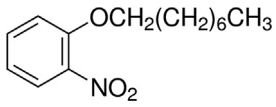

Fig. 3. The structure of 2-nitrophenyl octyl ether (NPOE).

2. Experimental

2.1. Instruments

Jenway digital ion analyzer model 3330 (Essex, UK) with Ag/AgCl double junction reference electrode no. Z113107-1EAPW (Aldrich Chemical Co. Steinheim, Germany) and pH glass electrode (Jenway, Essex, UK) no. 924005-BO3-Q11C. Magnetic stirrer, Bandelin Sonorox, Rx510S (Budapest, Hungary).

2.2. Materials

2.2.1. Reference samples

A pure sample of sulfacetamide sodium monohydrate was kindly offered by the Egyptian International Pharmaceutical Industries Company (EIPICO), Egypt and its purity was checked and found to be 99.96 ± 0.722 according to BP method (titrimetric method) [1]. Prednisolone acetate was kindly supplied by Pharonia pharmaceuitcals, Egypt and its purity was checked and found to be 100.01 ± 0.525 according to BP method (spectrophotometric method) [1].

2.2.2. Pharmaceutical formulations

Blephamide® ophthalmic suspension, batch No.1505211, manufactured by the Egyptian International Pharmaceutical Industries Company (EIPICO). It is labeled to contain 100 mg sulfacetamide sodium and 2 mg prednisolone acetate per one mL.

Ocusol® 10%, batch No.5518007& Ocusol® 20% ophthalmic solution, batch No.6519001, Both dosage forms were manufactured by Alexandria Co. for Pharmaceuticals & Chemical Industries. They are labeled to contain 100 mg and 200 mg sulfacetamide sodium per one mL, respectively.

The pharmaceutical formulations were purchased from local pharmacies.

2.3. Chemicals and solvents

All chemicals and solvents used were of analytical grade. High molecular weight Polyvinyl chloride (PVC), tetradodecylammonium bromide (TDB), tetraheptylammonium bromide (THB), 2-nitrophenyl octyl ether (NPOE), dibutyl sebaceate (DBS) and tetrahydrofuran (THF) were obtained from (Sigma Aldrich, Steinheim, Germany). Malachite green oxalate was obtained from (Alpha chemika, Mumbai, India). Potassium chloride, hydrochloric acid, sodium hydroxide and sodium dihydrogen phosphate were supplied from (El-Nasr pharmaceutical chemical company, Cairo, Egypt). Oxybuprocaine HCl was kindly supplied from (EIPICO, Cairo, Egypt). Distilled deionized water was supplied from (Alpha pure labs, Cairo, Egypt). Phosphate buffer, pH 6, was prepared according to BP by dissolving 6.8 g of sodium dihydrogen phosphate in water and diluting to 1000 mL with water then adjustment the pH with strong sodium hydroxide solution [1].

2.3.1. Rabbit aqueous humor

It was collected from ten albino rabbits. Two drops of 0.4% solution of oxybuprocaine HCl (Local anesthetic) were instilled into rabbit's eyes. Samples of aqueous humor were immediately removed from the anterior chamber of each eye using a 26- gauge needle attached to 1 mL tuberculin syringe. The procedure was repeated 2 times a day for about 3–5 days till the required volume was collected. The samples were stored frozen until the experiment was carried out. After removal of aqueous humor samples at each time interval, the rabbits were sacrificed [18].

2.4. Standard solutions

(a) *Sulfacetamide sodium stock standard solution (1×10^{-2} M)*

The solution was prepared by transferring 0.254 g of sulfacetamide sodium into a 100-mL volumetric flask, dissolved then completed to the mark with phosphate buffer, pH 6.

(b) *Sulfacetamide sodium working standard solutions (1×10^{-6}–1×10^{-3} M)*

Different solutions of sulfacetamide sodium having variant strengths (1×10^{-6}–1×10^{-3} M) were prepared by serial dilutions from the stock solution then completing to the mark with phosphate buffer, pH 6.

(c) *Prednisolone acetate stock standard solution (1×10^{-2} M)*

The solution was prepared by transferring 0.402 g of prednisolone acetate into a 100-mL volumetric flask, dissolved and completed to the mark with phosphate buffer, pH 6.

(d) *Prednisolone acetate working standard solutions (1×10^{-4}& 2×10^{-3} & $\times 0^{-3}$ M)*

Different solutions of prednisolone acetate having variant strengths (1×10^{-4} & 2×10^{-3} & 1×10^{-3} M) were prepared by serial dilutions from the stock solution then completing to the mark with phosphate buffer, pH 6.

2.5. Procedures

2.5.1. Fabrication of the membrane sensor

In a glass Petri dish (5-cm diameter), 0.4 mL of NPOE was added to 190 mg of PVC and 10 mg of TDB. The mixture was mixed and dissolved in 10 mL of THF then the Petri dish was enveloped with a filter paper. The solvent was allowed to evaporate overnight at room temperature. A master membrane having a thickness of about 0.1 mm was obtained.

2.5.2. Electrode assembly

From master membrane, a disk (about 8-mm diameter) was cut by a cork borer and then was attached using THF to a transposable PVC tip that was clipped into the end of the electrode glass part. The electrode was then filled with equal volumes of 1×10^{-3} M sulfacetamide sodium and 1×10^{-3} M potassium chloride (dissolved in phosphate buffer pH 6) which is used as an internal reference solution. A wire of Ag/AgCl (1-mm diameter) was added in this solution as an internal reference electrode. Conditioning of the sensor was done by soaking into a 1×10^{-3} M sulfacetamide sodium standard solution for 24 h.

2.5.3. Sensor calibration

The sensor in conjugation with a double-junction Ag/AgCl reference electrode, was immersed in sulfacetamide sodium standard solutions in the range of (1×10^{-6}–1×10^{-2} M). It was allowed to equilibrate while stirring until achieving a constant reading of the potentiometer. Then, the electromotive forces (e.m.f) were measured at room temperature. The sensor was washed with phosphate buffer, pH 6, before and after each run until reaching a constant potential. Calibration graph was plotted relating the recorded electrode potential from the proposed sensor versus the – log molar concentrations of sulfacetamide sodium. The regression equation for the linear part of the curve was computed and used for the determination of unknown sulfacetamide sodium concentrations.

2.5.4. Estimation of the slope, response time and operative life of the proposed sensor

The electrochemical characteristics of developed sensor were calculated according to the IUPAC guidelines [19].

2.5.5. Effect of pH and temperature

The effect of pH on the potential values of the sensor was determined using 10^{-3} M and 10^{-2} M solutions of sulfacetamide sodium in the pH range of 2–12.

The potential values shown by the studied electrode as a function of temperature in the range of 20 °C, 30 °C and 40 °C were monitored and the obtained potential was recorded at each temperature.

2.5.6. Sensor selectivity

The sensor selectivity was studied regarding effect of interfering ions, co-formulated drug of sulfacetamide sodium in the dosage form (prednisolone acetate), and rabbit aqueous humor.

(a) *Interfering ions*

The potential response of the developed sensor in the presence of some foreign related substances was estimated. The potentiometric selectivity coefficient ($K^{Pot}_{\text{sulfacetamide sodium, interferernt}}$) was calculated to evaluate to which degree a related substance would interfere with the electrode response to its primary ion. The selectivity coefficients were calculated using the separate solutions method (SSM) [20] using the following equation:

$$-\log(K^{Pot}_{\text{Primary ion,interferernt}}) = E_1 - E_2/S$$

where E_1 is the potential measured in 10^{-3} M of the sulfacetamide sodium solution, E_2 is the potential measured in 10^{-3} M of the interferent solution and S is the slope of the proposed sensor.

(b) *Study of laboratory prepared mixtures*

For further assessment of the electrode selectivity in the presence of prednisolone acetate, five different laboratory prepared mixtures were prepared of sulfacetamide sodium and prednisolone acetate in different ratios. Different volumes of sulfacetamide sodium (1×10^{-2} M prepared in phosphate buffer, pH 6) and prednisolone acetate (1×10^{-2} M prepared in phosphate buffer, pH 6) were accurately measured and transferred into 25-mL volumetric flasks. The volumes were then completed to the mark by phosphate buffer, pH 6. The potential of each laboratory prepared mixture was recorded by the proposed sensor and the concentration of sulfacetamide sodium was calculated using the corresponding regression equation.

(c) *Rabbit aqueous humor*

An aliquot of 0.5 mL of 10^{-2} M and 10^{-3} M standard drug solution was transferred into two separate 5-mL volumetric flasks containing 4.5 mL of the collected aqueous humor and were vortexed for one min. The potentiometric measurements were performed using the proposed sensor and the concentration of sulfacetamide sodium was calculated using the corresponding regression equation.

2.5.7. Potentiometric determination of sulfacetamide sodium in blephamide® ophthalmic suspension and ocusol® eye drops (10% & 20%)

Aliquots of 0.64 mL of Blephamide® ophthalmic suspension and Ocusol® 10% eye drops and 0.32 mL of Ocusol® 20% eye drops were transferred to 25-mL volumetric flasks. The volume was brought to the mark with phosphate buffer, pH 6 and the flasks were shaken well to reach a final concentration of 10^{-2} M sulfacetamide sodium.

The prepared electrode in conjunction with the double junction Ag/AgCl reference electrode was immersed in the prepared solution. The resulting potential was recorded, and the respective concentration was calculated from the corresponding regression equation.

3. Results and discussion

From the literature review survey, it was obvious that sulfacetamide sodium was extensively analyzed by different analytical techniques. We tried determination of the drug by the potentiometric one due to the advantages of this techniques regarding its selectivity, sensitivity, being non costly and eco-friendly method of analysis. So, we worked in this study to suggest new fabricated electrode with competitive properties after several designs of different ones.

3.1. Sensor fabrication

(a) *PVC matrix*

It has been stated that a PVC matrix is a regular polymeric matrix to immobilize the sensor and to achieve the formation of highly stable complexes. However, PVC needs plasticization [21].

(b) *Plasticizers*

The plasticizer acts as a liquefying agent by allowing a homogenous solubilization that makes the membrane material workable. It also modifies the distribution of the ion exchanger and sustains these features for continued use [22]. In the present work, some plasticizers (NPOE and DBS) were examined. It is well known that the nature of the plasticizer used is one of the important factors that affect sensitivity and selectivity of ion-selective electrodes [23].The optimum plasticizer for the developed sensor was found to be NPOE. The values of its dielectric constants, lipophilicity and molecular weight (ε_r 24, P_{TLC} 10.2, M.W. 435) favors its use to be a suitable plasticizer for this membrane. Thus, it delivers the higher selectivity and sensitivity [24].

(c) *Ion exchangers*

The lipophilic ionic sites in the ion exchanger encourage the interfacial ion-exchange kinetics through providing mobile ionic sites in the electrode matrix [23]. In the present work, sulfacetamide sodium acts as an anion in approximately neutral medium. Thus, the ion selective

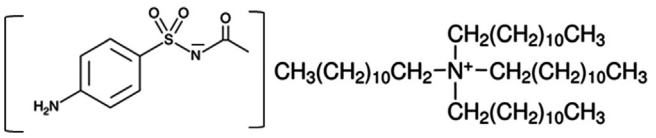

Fig. 4. The structure of an ion association complex of the anionic sulfacetamide sodium and the cationic tetradodecylammonium.

Table 1
The electrochemical characteristics of the developed sensor.

Parameter	The Response
Slope (mV/decade)	−51.486
S.E. of slope	0.470
Intercept (mV)	95.829
S.E. of intercept	0.139
Correlation coefficient(r)	0.9999
Concentration range (M)	$10^{-4.5}$–10^{-2}
Working pH range	5–7
Response time (s)	10–15
Stability (weeks)	4
Accuracy (Mean recovery% ± SD)[a]	100.75 ± 1.989
Precision	
Repeatability (RSD%)[b]	1.380
Intermediate precision (RSD%)[c]	1.466
LOD (M)[d]	2.23×10^{-5}

[a] Average of five determinations.
[b] Repeatability: the intraday precision (n = 3 × 3), average of three concentrations were repeated three times within the day.
[c] Intermediate precision: the interday precision (n = 3 × 3), average of three concentrations were repeated three times on three consecutive days.
[d] LOD (Limit of detection) was measured by interception of the extrapolated arms of Fig. 5.

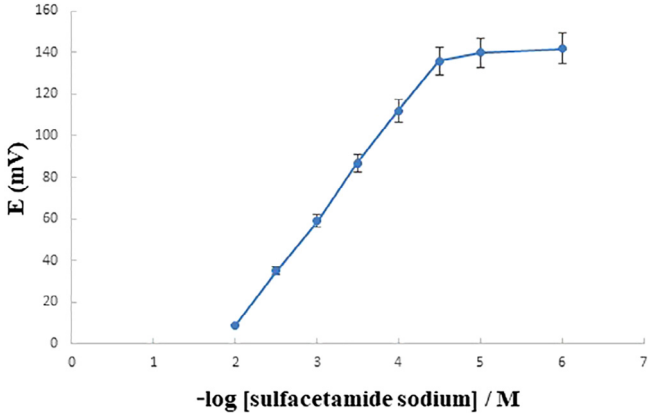

Fig. 5. Profile of the potential in mV versus – Log sulfacetamide sodium molar concentration using the developed sensor [1×10^{-6} M–1×10^{-2} M].

electrode membrane must display anion exchange capacity. This was achieved using a lipophilic anionic exchanger; tetradodecylammonium bromide (TDB), where the membrane was initially conditioned in 1×10^{-3} M sulfacetamide sodium for 1 day to replace the original exchangeable counter ion (Br^-) of the ion exchanger with the drug, Fig. 4. Preliminary trials of some anionic exchangers were performed using tetraheptylammonium bromide (THB) and malachite green oxalate. It was found that the obtained potentials showed a non-reproducible slope, lower linearity range (10^{-3} M–10^{-2} M) and short operative life. On the contrary, the results obtained using the developed tetradodecylammonium bromide (TDB) sensor showed great reproducibility, high accuracy and selectivity for drug determination.

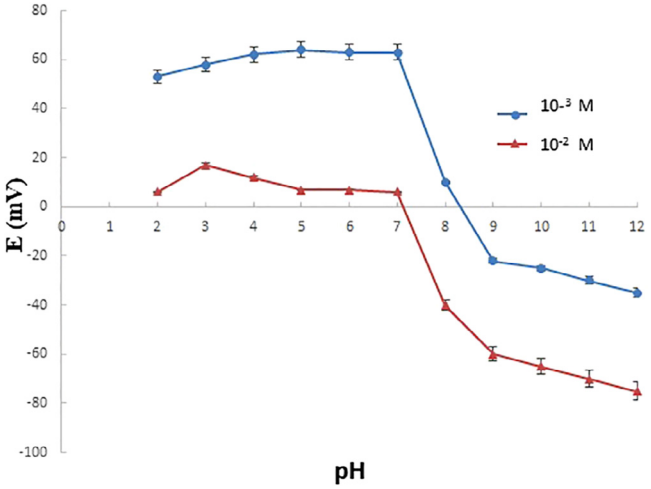

Fig. 6. Effect of pH on the response of the developed sensor.

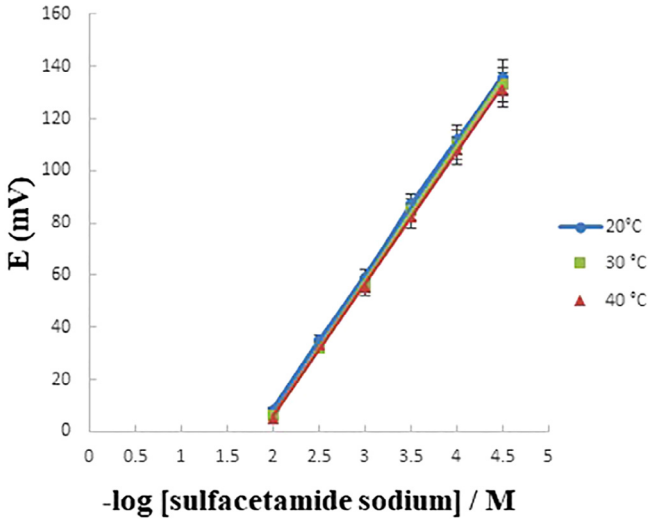

Fig. 7. Effect of temperature on the response of the developed sensor.

Table 2
Potentiometric Selectivity Coefficients ($K^{pot.}$) of the developed sensor using separate solutions method (SSM).

Interferent (10^{-3} M)	Selectivity Coefficients ($K^{pot.}$)
Prednisolone acetate	2.31×10^{-3}
Sulfanilamide	5.63×10^{-2}
Dapsone	2.63×10^{-3}
Benzalkonium chloride	1.35×10^{-3}
Boric acid	2.61×10^{-3}
Phosphate	3.55×10^{-4}

3.2. Sensor calibration and response time

The electrochemical characteristics of the developed sensor were calculated according to IUPAC guidelines [19]. Table 1 shows the electrochemical characteristics for the proposed sensor. Typical calibration graph is shown in Fig. 5. The slope was calculated from the linear part of the calibration graph which was 51.486 mV/ decade for the proposed sensor. The reason for deviation from the ideal Nernstian slope (60 mV) is that the electrode responds to the activity of the drug anion rather than its concentration. The sensor showed constant potential readings within ± 2 mV from day to day and the slope didn't alter by more than 3 mV. The required time for the sensor to reach

Table 3
Determination of sulfacetamide sodium in laboratory prepared mixtures containing different ratios of sulfacetamide sodium and prednisolone acetate by the developed sensor.

Ratio of Sulfacetamide sodium:Prednisolone acetate	Sulfacetamide sodium Concentration (M)	Prednisolone acetate Concentration (M)	Sulfacetamide sodium Recovery %
50:1*	5×10^{-3}	10^{-4}	101.30
1:1	10^{-3}	10^{-3}	103.67
10:1	10^{-3}	10^{-4}	102.01
1:2	10^{-3}	2×10^{-3}	100.33
2:1	2×10^{-3}	10^{-3}	99.26

* Ratio in Blephamide® ophthalmic suspension.

Table 4
Determination of sulfacetamide sodium in spiked rabbit aqueous humor by the developed sensor.

Sulfacetamide sodium concentration	Recovery* % ± SD
10^{-3} M	99.76 ± 1.215
10^{-4} M	100.74 ± 0.982

* Average of three determinations.

Table 5
Determination of sulfacetamide sodium in Blephamide® ophthalmic suspension and Ocusol® 10% & 20% eye drops by the developed sensor.

Pharmaceutical formulation	Found * % ± SD
Blephamide®	99.84 ± 0.788
Ocusol® 10%	101.89 ± 0.889
Ocusol® 20%	101.99 ± 0.976

* Average of five determinations.

values within ± 1 mV of the final equilibrium was found to be 10–15 s. The response time rises with increasing the concentrations.

3.3. Effect of pH and temperature

For quantitative analysis with ISEs, studies were performed to reach the best experimental conditions. The effect of pH on the response of the investigated sensor was evaluated. Fig. 6 shows the potential-pH profile of 1×10^{-2} and 1×10^{-3} M sulfacetamide sodium solutions using the sensor. It seems that the response of sensor was almost constant in solutions of pH values 5–7. Consequently, the pH range of 5–7 was supposed to be the optimum working pH range for the sensor.

When studying the effect of temperature, the investigated sensor showed a slight decrease in its response as the temperature increased in the range of 20 °C to 40 °C. Though, the calibration graphs obtained at these temperatures were parallel, demonstrating thermal stability of the developed sensor up to 40 °C, Fig. 7.

3.4. Sensor selectivity

(a) *Interfering ions*

The effect of related substances on the performance of the sensor was studied by the separate solutions method (SSM) [20]. The lower the selectivity coefficient value, the more confidence the electrode membrane isn't attacked by the interfering ions. The response of the sensor in the presence of its co-formulated drug prednisolone acetate, its official stated impurities and its susceptible excipients was evaluated. The results of the calculated selectivity coefficients showed that the proposed sensor demonstrated high selectivity and it was obvious that there was no significant interference from the interfering species, Table 2.

(b) *Study of laboratory prepared mixture*

Laboratory prepared mixtures were prepared with different ratios of sulfacetamide sodium and its co-formulated drug (prednisolone acetate), including their ratio in the ophthalmic suspension. The results showed that the proposed sensor can be effectively used for the determination of sulfacetamide sodium in the presence of prednisolone acetate with no need for prior separation, Table 3.

(c) *Rabbit aqueous humor*

Rabbit aqueous humor is considered a suitable different matrix for estimation of the electrode selectivity as the studied drug (sulfacetamide sodium) is used mainly in ophthalmic preparations for topical use as mentioned before. For determination of sulfacetamide sodium in spiked rabbit aqueous humor, it was found that the sensor was reliable and gave stable results with very good accuracy and high percentage recovery for the determination of sulfacetamide sodium without any need for extraction procedures, as represented in Table 4. The response time of the sensor was instant (within 15 sec). It means that the proposed sensor can be applied successfully to in vitro and clinical studies.

Table 6
Statistical comparison of the results obtained by the proposed ion selective electrode method for the determination of sulfacetamide sodium and those obtained by the official methods.

Item	The developed Sensor (Blephamide®)	Official method [a]	The developed sensor (Ocusol® 10%)	Official method[b]	The developed Sensor (Ocusol® 20%)	Official method[b]
Mean	99.84	99.31	101.89	101.04	101.99	100.63
S.D.	0.788	0.961	0.889	0.772	0.976	1.559
n	5	5	5	5	5	5
Variance	0.621	0.923	0.789	0.596	0.953	2.431
F test[c]	1.486 (6.94)		1.324 (6.94)		2.551 (6.94)	
Student's *t* test[c]	0.946 (2.306)		1.521 (2.306)		1.909 (2.306)	

[a] HPLC method using C_{18} column with mobile phase containing a mixture of (water:methanol:glacial acetic acid) (89:10:1) for determination of sulfacetamide sodium and (water:acetonitrile) (60:40) for determination of prednisolone acetate, flow rate 1.5 mL/min and detection wavelength at 254 nm.

[b] HPLC method using C_{18} column with mobile phase containing a mixture of (water:methanol:glacial acetic acid) (89:10:1), flow rate 1.5 mL/min and detection wavelength at 254 nm.

[c] Figures between parenthesis are the corresponding tabulated values (P = 0.05).

3.5. Potentiometric determination of sulfacetamide sodium in its pharmaceutical dosage forms

The proposed sensor was employed for analysis of sulfacetamide sodium in its pharmaceutical formulations (Blephamide® ophthalmic suspension and Ocusol® 10% & 20% eye drops. The results demonstrated great accuracy of the proposed sensor for the determination of the sulfacetamide sodium in its dosage forms. This indicates no interference from its co-formulated drug in the dosage form (prednisolone acetate) and any excipients that may be found in the dosage forms, Table 5.

3.6. Statistical comparison of the results obtained from the proposed sensor with those obtained from the official methods

The pharmaceutical dosage forms were analyzed by the developed potentiometric method and the United States Pharmacopeia official methods [25]. Statistical analysis of the results (suggested& official ones) was done using t and F values [26]. No significant difference was obtained with respect to both accuracy and precision, Table 6.

4. Conclusions

This work presents a study to develop and validate optimized ion-selective membrane sensor for the determination of sulfacetamide sodium. The response of the fabricated sensor is sufficiently accurate and precise. It demonstrates good selectivity of the sensor for the determination of sulfacetamide sodium in its pure form, pharmaceutical formulations and in biological fluid (Rabbit aqueous humor). Furthermore, the proposed sensor offers advantages of removing any need for drug pretreatment or separation steps, providing simplicity in design, being economic one and could compete with the many sophisticated methods presently available. In general, the ISEs are considered to be one of the green analytical techniques. Therefore, the developed sensor can be used for the routine analysis of sulfacetamide sodium in quality control laboratories.

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