

Determination of Salicylate by Selective Poly(vinylchloride) Membrane Electrode Based on *N,N'*-1,4-Butylene Bis(3-methyl salicylidene iminato) Copper(II)

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A new salicylate-selective electrode based on the complex *N,N'*-1,4-butylene bis(3-methyl salicylidene iminato) copper(II) as the membrane carrier was developed. The electrode exhibits a good Nernstian slope of -59.1 ± 1.0 mV/decade and a linear range of 1.0×10^{-6} -1.0 M for salicylate. The limit of detection was 5.0×10^{-7} M. It has a fast response time 10 s and can be used for more than three months. The selective coefficients were determined by the fixed interference method (FIM) and could be used in the pH range 4.5-10.5. It was employed as an indicator electrode for direct determination of salicylate in pharmaceutical samples.

Key Words : Salicylate, Salicylate-selective electrode, Potentiometry, Ionophore

Introduction

The development of PVC membranes has made the original liquid membrane electrode configuration virtually redundant and has led to potentiometric sensors based on polymer membranes being available commercially to sense ions such as calcium, magnesium, nitrate, bicarbonate. It should be noted that many of the biologically important ions are included in this list and so potentiometric sensors are used extensively in the analysis of biological fluids.

Perhaps the most significant advance in liquid membrane electrodes, other than the original discovery, occurred in 1970 when it was shown that the organic liquid of the liquid membrane ion-selective electrode (ISE) could be immobilized into poly(vinyl chloride) to produce a polymer film with sensing properties for calcium as good as, if not better than, the liquid membrane itself.¹

Construction and then application of ion-selective electrode as a potentiometric sensor offers interesting advantages such as simplicity, speed, fast response, low cost, wide linearity range and procedure. These characteristics have inevitably led to sensors for ionic species.² If the attraction is purely electrostatic; the partitioning of anions from the aqueous sample solution into the ISE membrane is simply dependent on the lipophilicity of the anions.^{3,4} Selectivity of these classical ion exchangers depends on the lipophilicity of the anions, with more lipophilic anions responding the best. The most important recognition elements that can be utilized in the development of ISEs involve specific metal-ligand interaction.⁵ The demand for ionophores with either new or improved selectivities in the field of ion-selective electrodes is high, particularly in the area of anion-selective electrodes. A strong interaction between the ionophore and the anion is required in order to successfully complex anions in a selective fashion. Complexes of several metal ions with different ligands, as ionophores for anions, have been observed to show such specific metal ligand interactions and induce anion selectivities in the membranes that differ

somewhat from the classical anion exchangers.⁶⁻⁸

Salicylic acid is one of the common metabolites of acetylsalicylic acid (aspirin), which is widely used as an analgesic and inflammatory agent and, recently, also as a preventive of heart attacks.⁹ The free acid is widely used as an antiseptic and a preservative for foods, and in cases of acute salicylate poisoning, where knowledge of the plasma salicylate level and of its rate of change provides a valuable indication of the severity of poisoning, and a very useful guide to the type of treatment required.

In recently, several new salicylate-selective membrane electrodes have been reported by using a variety of ion carriers.¹⁰⁻¹⁴ For the PVC membrane ion-selective electrode, the complex as an ionophore reversibly combines the anions in a selective fashion, mainly owing to a strong interaction between the ionophore and the anions. Complexes of several central metal ions with different ligands have been reported to display such specific metal-ligand interactions and to induce anion selectivity of the membranes. These complexes differ from the classical anion exchanger, for instance, quaternary ammonium or phosphonium salts, with which the membrane selectivity is mainly dominated by the free energy of hydration of ions involved. Some Sn(IV) compounds have been used as the ionophore for PVC membrane electrodes with an anti-Hofmeister selective pattern; most of them are Sn(IV) porphyrin and phthalocyanine complexes, and most of them are tetra-coordinate and plane molecules.¹³ A salicylate-selective electrode made with heptyl-4-trifluoroacetylbezoate as a neutral carrier was successfully applied for the determination of salicylate in blood serum.¹² Also, the electrode is prepared by incorporating 5,10,15,20-tetraphenyl(porphyrinato)tin(IV) chloride into a plasticized poly(vinyl chloride) membrane. This sensor exhibits an anti-Hofmeister selectivity pattern, with high specificity for salicylate over lipophilic organic anions (perchlorate, periodate, thiocyanate, iodide, etc.) and biological organic anions (citrate, lactate, acetate).¹⁵ The development of a suitable salicylate-selective electrode, would enable the detection of

“free” salicylate in samples and could aid researcher in studying the pharmacological role of this drug.¹⁵

The present work describes the results obtained from a study of salicylate-selective electrode based on *N,N'*-1,4-butylene bis(3-methyl salicylidene iminato) copper(II).

Experimental Section

Reagents. PVC of high relative molecular weight, tri-octylmethyl ammonium chloride (TOMAC) and dioctyl phthalate (DOP) were used as received from Aldrich. The ionophore of *N,N'*-1,4-butylene bis(3-methyl salicylidene iminato) copper(II) (Fig. 1) was synthesized and used after purification. Potassium or sodium salts of all anions, tetrahydrofuran (THF) and all other chemicals were of highest purity available from Merck, and were used without further purification, except THF, which was distilled before use. All of the solutions were prepared using doubly distilled deionized water. The pH adjustments were made with dilute phosphoric acid and sodium hydroxide. A stock solution of salicylate, was prepared by dissolving the appropriate amount of sodium salicylate in 100 mL of water. Working solutions were prepared by successive dilutions with water. All of the working solutions were buffered at pH 7.0, using phosphate buffer solution.

Synthesis of ionophore. Complex and related Schiff base were prepared in accordance with the previously reported procedures.^{16,17} *N,N'*-1,4-butylene bis(3-methyl salicylidene iminato) copper(II): Green crystals, m.p. = 326–329 °C, IR (cm⁻¹, KBr): 3007 (m), 2920 (m), 2860 (m), 1620 (s), 1551 (s), 1475 (m), 1320 (s), 1216 (m), 1047 (m), 836 (m), 514 (m). Mass (m/c): 388 (M+3, 10.6), 387 (M+2, 41.8), 386 (M+1, 19.7), 385 (M, 73), 324 (5.7), 189 (69.7), 172 (31.1), 146 (100), 134 (45.1), 121 (52.5), 91 (67.2), 77 (36.1), Uv (CH₃CN): λ_{max}: 292.7 nm.

For the preparation of pharmaceutical samples, tablets of three different samples of aspirin were finely powdered. A precisely weighed portion of each sample was refluxed with 50 mL of 1.0 M NaOH for 1 h. After being filtered, the solution was diluted to 250 mL in a volumetric flask and used for the determination of salicylate content by potentiometric and spectrophotometric methods.

Electrode preparation. A mixture of PVC, DOP as plasticizer and TOMAC as an additive with lipophilic cation were dissolved in a minimal amount of tetrahydrofuran (THF). The PVC-THF solution was mixed with *N,N'*-1,4-

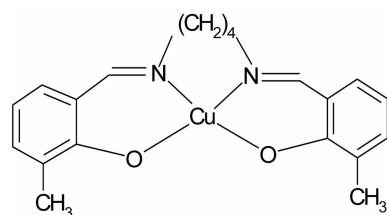
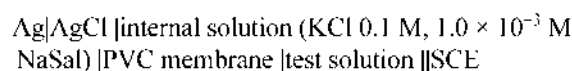


Figure 1. Structural representation of the compound of *N,N'*-1,4-butylene bis(3-methyl salicylidene iminato) copper(II) used as ionophore in the PVC-membrane sal-selective electrode.

butylene bis(3-methyl salicylidene iminato) copper(II) [CuL]. The resulting mixture was poured into a small flat bottom dish, covered with a filter paper and the solvent was allowed to evaporate at room temperature. The resulting membrane (ca. 0.2 mm thick) was then sectioned with a cork borer and mounted across the opening of a PVC tube of about 7 mm i.d. and 1.5 cm length using a glue of PVC in THF. The PVC tube with the membrane was then incorporated into a silver-silver chloride wire electrode. The electrode was then filled with an internal solution of 0.1 M KCl and sodium salicylate 1.0×10^{-3} M.

Potential measurement and calibration. The electrochemical system for this electrode can be represented as follows:



All potentials were measured at 25 ± 1 °C using Metrohm model 691pH/mV meter. A saturated calomel electrode (SCE, Metrohm) with a fiber junction was used as the external reference electrode. Activities were calculated according to the Debye-Hückle procedure,¹⁸ also, for the calibration curve, concentration instead of activity was used. The pH of the sample solution was monitored simultaneously with a conventional glass pH electrode (Metrohm).

Before starting the measurements, the electrode was preconditioned in stirred water until a steady potential was obtained. The performance of the electrode was investigated by measuring its potential in sodium salicylate solutions prepared in the concentration range 1.0×10^{-7} –1.0 M by serial dilution at a constant pH = 7. All solutions were freshly prepared by dilution from the stock standard solution, 2.0 M, with doubly distilled water. The solutions were stirred and potential readings recorded when they became stable. The data were plotted as observed potential vs. the logarithm on the salicylate concentration.

Results and Discussion

The influence of membrane composition. The plasticized PVC-based membrane electrode containing the ionophore generates a stable potential response in solution containing salicylate. The electrode suffered from long response times and potential drift which was assumed to be due to high membrane resistance. The response of the electrode was improved by addition of lipophilic salts such as TOMAC to the membrane not only reduces the membrane resistance but also enhances the response behavior and selectivity and reduce interferences from lipophilic sample anions.^{19,20} The membrane without the ionophore displayed insignificant selectivity toward salicylate whereas, in the presence of the ionophore, the membrane shows remarkable selectivity for salicylate over most common inorganic and organic anions. The preferential response toward salicylate is believed to be associated with the coordination of salicylate with central metal ion of the carrier and the lipophilicity of the anion. It is well-known that the sensi-

Table 1. Optimized membrane compositions and their potentiometric response properties in salicylate-selective electrode. Values in table are mass ratio in percent.

No	%PVC	%DOP	%Ionophore	%Additive	Slope, mV/decade	Linear dynamic range, M
1	32.5	62	5	0.5	-42	1.0×10^{-4} - 1.0×10^{-1}
2	32	61	6	1	-47.1	1.0×10^{-4} - 1.0×10^{-1}
3	31	60	7	2	-46.7	1.0×10^{-5} - 1.0×10^{-1}
4	31	61	6	2	-59.1	1.0×10^{-6} -1.0
5	32	61	5	2	-59.9	1.0×10^{-5} -1.0

tivity and selectivity obtained for a given ionophore depends significantly on the membrane condition.²¹⁻²⁴ Several membrane compositions were investigated by varying the proportions of PVC, DOP, membrane active material, [CuL] and TOMAC. Irrespective of ionophore concentration the slope was relatively larger when DOP/PVC weight ratio was approximately 2.0. It was also observed that the potentiometric response of the electrode toward salicylate ion depended on the concentration of the ionophore incorporated within the membrane. Increasing the amount of [CuL], up to 6% resulted in membranes for which slopes were larger and the linear range wider.

The potentiometric response of the membrane was greatly improved by the presence of the lipophilic cationic additive, TOMAC. Better response characteristics, *i.e.* Nernstian response and improved selectivity, were usually observed with an ionophore/TOMAC weight ratio of approximately 3.0 which corresponds to a mole ratio of approximately 3.1. The presence of lipophilic ionic sites is beneficial for both neutral carrier and charged carrier-based ion-selective electrodes.^{25,26}

Among the different compositions studied (Table 1) responses were best for the membrane incorporating 31%PVC, 61%DOP, 2% additive and 6% [CuL]. The composition was, therefore, used to study the performance of the electrode, *viz.* working concentration range, sensitivity, selectivity, life time, response time, and effect of pH. The characteristic properties of the optimized membrane are summarized in Table 2.

Over the concentration range 1.0×10^{-6} -1.0 M of salicylate in the calibration solution, the electrode potential response was linear with the concentration of salicylate. The calibration curve slope was -59.1 ± 1.0 mV/p[Sal] and the detection limit, calculated as recommended by the IUPAC,

Table 2. Characteristics of optimized Sal-ISE

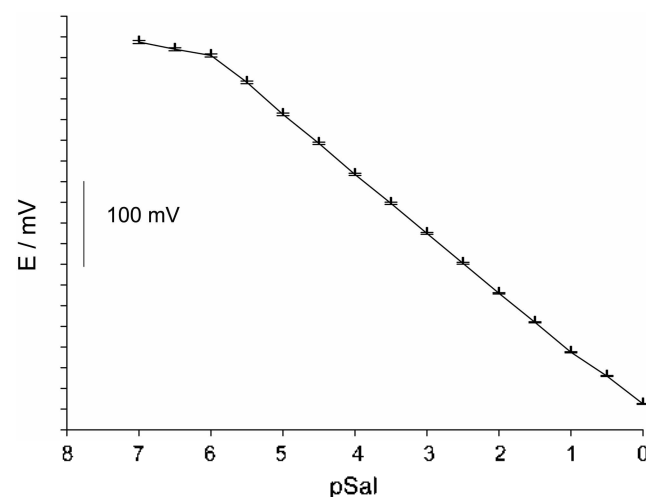
Linear range / M	1.0×10^{-6} -1.0
Slope / mVdecade ⁻¹	-59.1
pH range	4.5-10.5
Precision	At concentrations of 1.0×10^{-2} , 1.0×10^{-3} and 1.0×10^{-1} M sal ⁻ standard deviations were of ± 0.5 , ± 0.8 and ± 0.8 mV respectively.
Detection limit / M	5.0×10^{-7}
Life time / month	> 3
Response time / s	5-10

was 5.0×10^{-7} M.²⁷ It is below the normal salicylate concentration in whole blood, plasma and serum. In practice, slopes of between 55 and 59 mV decade⁻¹ are referred to as Nernstian for analytical purposes.^{28,29} The potentiometric response characteristics of the plasticized PVC-based electrode, incorporating *N,N'*-1,4-butylene bis(3-methyl salicylidene iminato) copper(II) [CuL], towards salicylate ion is shown in Figure 2.

Response characteristics of the electrodes. The influence of the concentration of internal solution on the potential response of the salicylate-selective electrode was studied and the results showed the concentration of the internal solution doesn't cause any significant difference in the potential response of the electrodes, except for an expected change in the intercept of the resulting Nernstian plots.

The effect of pH of the test solution on the response of the membrane electrodes was examined at two salicylate concentrations. As illustrated in Figure 3 for 1.0×10^{-3} M and 1.0×10^{-2} M salicylate, the potentials remain constant from pH of about 4.5-10.5. The results show that the sensor is suitable for salicylate determination in wide pH range of 4.5-10.5. In high pH media, probably OH⁻ will compete with salicylate ion, where as in acidic media (pH < 4.5), the drift in the potential may be due to the instability of the ionophore (complex of the copper with the ligand) due to the nitrogen and oxygen sites protonation.

The stability and reproducibility of the electrodes were also tested. The standard deviations of 20 replicate measure-

**Figure 2.** Potentiometric response of the salicylate-selective electrode to salicylate using optimized membrane electrode.

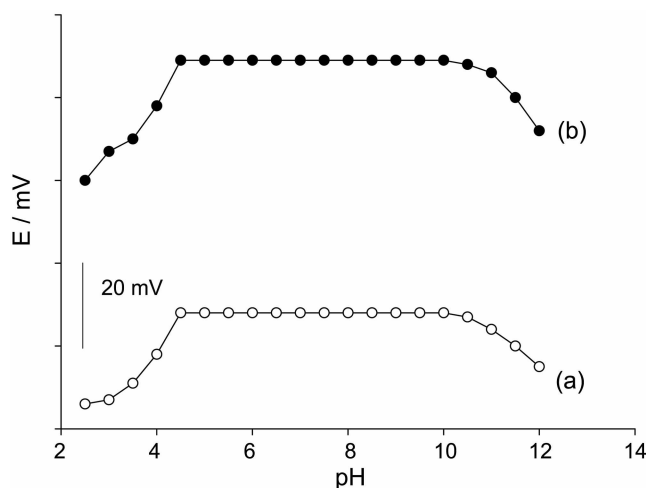


Figure 3. The pH response of the membrane electrode at (a) 1.0×10^{-3} M and (b) 1.0×10^{-2} M salicylate concentrations.

Table 3. Stability and reproducibility of the salicylate-selective electrode ($n = 5$)

Time (day)	Slope (mV/decade)	Linear range (M)
1	-59.1 ± 1.0	$1.0 \times 10^{-6} - 1.0$
7	-59.1 ± 1.0	$1.0 \times 10^{-6} - 1.0$
14	-59.1 ± 1.0	$1.0 \times 10^{-6} - 1.0$
21	-59.1 ± 1.2	$1.0 \times 10^{-6} - 1.0$
35	-58.8 ± 1.2	$1.0 \times 10^{-6} - 1.0$
49	-58.8 ± 1.5	$5.0 \times 10^{-6} - 1.0$
60	-58.5 ± 1.5	$5.0 \times 10^{-6} - 1 \times 10^{-1}$
70	-56.5 ± 1.5	$5.0 \times 10^{-6} - 1 \times 10^{-1}$
90	-55.5 ± 1.5	$1.0 \times 10^{-5} - 1 \times 10^{-1}$

ments for PVC sensor at 1.0×10^{-2} , 1.0×10^{-3} and 1.0×10^{-1} M salicylate were ± 0.5 , ± 0.8 and ± 0.8 mV respectively. The long-term stability of the electrode was studied by periodically re-calibrating in standard solutions and calculating the response slope over the range of 1.0×10^{-7} -1.0 M. The slopes of the electrode response were reproducible to within 4.0 mV/decade over a period of three months (Table 3).

The response time of the electrode was measured after successive immersion of the electrode in a series of salicylate solutions, in each of which the salicylate concentration increased tenfold, from 1.0×10^{-6} to 1.0×10^{-1} M. The static response time thus obtained was 5s for 1.0×10^{-1} M salicylate concentration. At lower concentrations, however, the response time was longer and reached 10 s for a salicylate concentration of 1.0×10^{-5} M. The actual potential versus time traces is shown in Figure 4. The potentials remained constant for approximately 5 min, after which a very slow change within the resolution of the meter was recorded. The sensing behavior of the membrane electrode did not depend on whether the potentials were recorded from low to high concentrations or vice versa.

Selectivity of the electrode. Potentiometric selectivity coefficient, defines the ability of an ion-selective electrode

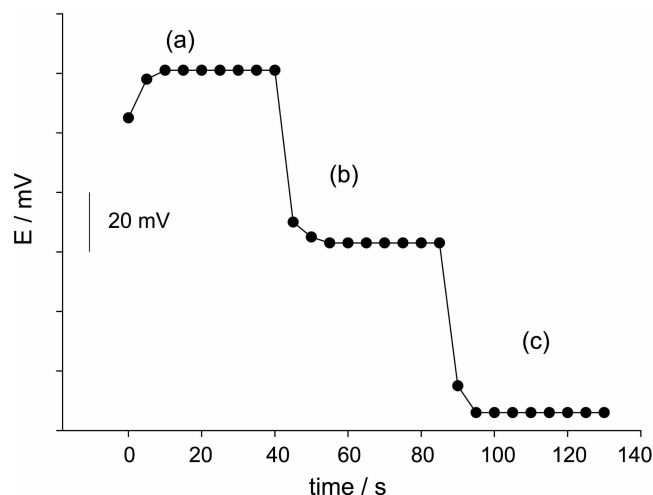


Figure 4. Response time of the membrane electrode for salicylate with change of concentration from (a) 1.0×10^{-5} M to 1.0×10^{-1} M (b) 1.0×10^{-4} M to 1.0×10^{-3} M (c) 1.0×10^{-3} M to 1.0×10^{-2} M.

to distinguish between different ions in the same solution. It is not identical to the similar term used in separation process. The selectivity coefficient should preferably be evaluated by measuring the response of an ion selective electrode in solutions of the primary ion, salicylate, and interfering ion, A (fixed interference method). The selectivity coefficient ($K^{\text{Pot}}_{\text{Sal},A}$) for various anions were evaluated by the mixed solution method with a fixed concentration of interference ion, and varying amounts of salicylate concentrations. Table 4 lists the potentiometric selectivity coefficient data of the sensor for several anions relative to salicylate. The selectivity coefficients clearly indicate that the electrode selective to salicylate over a number of other inorganic and organic anions. In this work, interference studies were made for F^- , Cl^- , Br^- , I^- , CH_3COO^- , SCN^- , CN^- and IO_3^- monovalent ions.

As can be seen from the Table 4, the most interfering anion to the electrode is perchlorate. The interfering effect of the ions is in the following order:

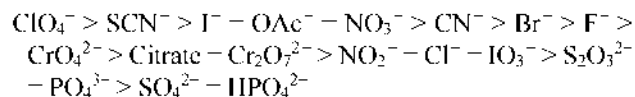


Table 4. Selectivity of coefficients, determined by use of the fixed interference method for the salicylate-selective electrode

Interfering Ion	$\log K^{\text{Pot}}_{\text{Sal},A}$	Interfering Ion	$\log K^{\text{Pot}}_{\text{Sal},A}$
F^-	-3.6	PO_4^{3-}	-4.1
Cl^-	-4.0	Citrate	-3.9
Br^-	-3.3	IO_3^-	-4.0
I^-	-3.0	SO_4^{2-}	-4.5
CN^-	-3.2	$\text{S}_2\text{O}_3^{2-}$	-4.1
SCN^-	-2.3	ClO_4^-	-0.2
$\text{Cr}_2\text{O}_7^{2-}$	-3.9	CrO_4^{2-}	-3.8
OAc^-	-3.0	NO_2^-	-4.0
NO_3^-	-3.0	HPO_4^{2-}	-4.5

Table 5. Comparison of the potentiometric parameters of the proposed sal-selective electrode with the other sal-selective electrodes

A ⁻	The proposed Sal-ISE	Ref: 13	Ref: 15	Ref: 19	Ref: 32	Ref: 33	Ref: 34
Nernstian slope, mV/decade	-59.1 ± 1.0	Ionophores (I,II respectively) ^a -58.9, -59.0	-55	Ionophores (I,II,III,IV,V respectively) ^b -50 ± 2, -54 ± 1, -53 ± 2, -41 ± 1, -41 ± 1	-60.0 ± 2	-54.3	-59.1
Linear range, M	1.0 × 10 ⁻⁶ - 1.0	Ionophores (I,II respectively) 1.0 × 10 ⁻⁶ - 1.0 × 10 ⁻¹ 1.0 × 10 ⁻⁵ - 1.0 × 10 ⁻¹	1.0 × 10 ⁻⁵ - 1.0 × 10 ⁻¹	(2.5 × 10 ⁻⁴ - 1 × 10 ⁻¹), (1 × 10 ⁻⁴ - 1 × 10 ⁻¹), (8 × 10 ⁻⁵ - 1 × 10 ⁻¹), (3 × 10 ⁻⁴ - 1 × 10 ⁻¹), (3 × 10 ⁻⁴ - 1 × 10 ⁻¹)	1 × 10 ⁻³ - 1 × 10 ⁻¹	5 × 10 ⁻⁶ - 1 × 10 ⁻¹	1.0 × 10 ⁻⁷ - 1.0 × 10 ⁻¹
Limit of detection, M	5.0 × 10 ⁻⁷	Ionophores (I,II respectively) 1.0 × 10 ⁻⁶ 4.0 × 10 ⁻⁶	1.0 × 10 ⁻⁵	8.0 × 10 ⁻⁵ , 4.0 × 10 ⁻⁵ , 1.3 × 10 ⁻⁵ , 8.0 × 10 ⁻⁵ , 8.0 × 10 ⁻⁵	6.0 × 10 ⁻⁴	1.9 × 10 ⁻⁶	1.0 × 10 ⁻⁷

^aIonophore I and II are [Al (salophen)] and [Sn (salophen)] respectively. ^bIonophore I, II, III, IV and V are [Aluminum Tetrakis-tert-butylphthalocyanine Chloride (P₆AlCl)], P₆Cu, P₆SnCl₂, P₆LuOAc, P₆DyOAc) respectively. Tetrakis-tert-butylphthalocyanine~P₆,

The selectivity coefficients of this electrode do not comply with the Hofmeister series, and show the selectivity which is near to a Hofmeister series. However, the lipophilicity of the anion still plays an important role and only the simultaneous consideration of both lipophilicity and interaction of the anion with Cu (complex stability, log K₁ = 10.6) allows one to explain the selectivity patterns.^{30,31} However, the selectivity coefficients of the salicylate-selective electrode against the other anions investigated are in good compliance with the literature data.^{13,15,19,32,33,35}

The fact that this electrode could be used over a wide pH range and good selectivity coefficient seems to be an advantage.

As it is evident from the data in Table 4 the electrode based on [CuL] has relatively high selectivity toward salicylate relative to anions such as nitrate, bromide, and several common anions. The compound of [CuL] seems to higher than interaction with the salicylate ion to any of the remainder anion tested. From the data given in Table 4, it is immediately obvious that the salicylate-ISE is highly selective with respect to other inorganic and organic anions. This is most probably due to the weak interaction between these anions and the ionophore.

Table 5 lists the linear range, detection limit, slope, response time and selectivity coefficients of some of other salicylate-selective electrodes against proposed salicylate-selective electrode for comparative purposes.^{13,15,19,32,33,34} As can be seen from the table, the selectivity coefficients obtained for the proposed electrode are superior to those reported for some other salicylate-selective electrodes listed in Table 5. It is noteworthy that the limit of detection, linear range, slope and response time of the proposed electrode are also considerably improved with respect to those the previously reported salicylate-selective electrodes.

Analytical applications. The high degree of salicylate selectivity exhibited by the electrode based on [CuL] carrier makes their potentially useful for monitoring concentration levels of salicylate in real samples. To assess the appli-

Table 6. Determination of salicylate in different Aspirin tablets samples (n = 10)

Aspirin samples (mg/Tablet)	Colorimetric method	ISE
100	97.3 ± 0.7	96.5 ± 1.0
325	321.0 ± 1.1	322.0 ± 1.2
500	472.0 ± 1.8	463.0 ± 2.1

cability of the membrane electrode real samples an attempt was made to determine salicylate in pharmaceutical preparations.

For the preparation of pharmaceutical samples, tablets of three different samples of aspirin were finely powdered. A precisely weighed portion of each sample was refluxed with 50 mL of 1.0 M NaOH for 1 h. After being filtered, the solution was diluted to 250 mL in a volumetric flask and used for the determination of salicylate content by potentiometric and spectrophotometric methods. The results are compared with the standard spectrophotometric method.³⁶ The results are presented in Table 6 indicate good agreement between the potentiometric and colorimetric procedures.

Conclusions

Taking all these discussed results into account, the proposed electrode was used for the analytical applications. This electrode is very easy to prepare and show high sensitivity and wide dynamic range. The high degree of salicylate selectivity by the electrode makes it potentially useful for monitoring concentration levels of salicylate in real samples, without the need for preconcentration or pretreatment steps and without significant interaction from other anionic species present in the samples.

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