

An Electrode of the Second Kind for Aspirin Determination in Tablet Formulations

Vinicius J. F. FERREIRA, Ana C. V. CAVALHEIRO, Enelton FAGNANI, Mercedes de MORAES, Leonardo PEZZA[†], Helena R. PEZZA and Cristo B. MELIOS

Instituto de Química-UNESP, C. P. 355, 14801-970, Araraquara, SP, Brazil

This paper describes the construction of an electrode of the second kind, Pt[Hg]Hg₂(Salic)₂/Graphite, sensitive to salicylate. This electrode responds to the salicylate ion with a sensitivity of 58.66 mV/decade over the range 6.0×10⁻⁴ – 1.0×10⁻¹ mol/l at pH 6.0 and an ionic strength of 0.500 – 3.00 mol/l, adjusted with NaClO₄. The electrode is easily constructed, shows a fast response time, is low in cost, has excellent response stability, and has a lifetime greater than 18 months, which is much longer than those reported earlier for other systems. The influence of 10 different carboxylate and inorganic anions on the electrode response showed that there was negligible interference by most of these ions. It was used to determine aspirin in tablets (after hydrolysis of acetylsalicylic acid to salicylate) by means of the standard additions method. The results obtained using this electrode for aspirin determination, in three different samples of antithermic drugs, compared favorably with the results given by the British Pharmacopoeia method.

Keywords Salicylate sensitive electrode, mercury-mercurous salicylate, pharmaceutical analysis, salicylate and acetylsalicylic acid determination

Salicylate and its analogues, such as acetylsalicylate (aspirin) are commonly used as with effective analgesics, and are available to the public in a wide variety of formulations. Aspirin, a prostaglandin biosynthesis inhibitor, is also an important antipyretic drug. Recently, a new therapeutic use has emerged based on its unique antiplatelet aggregation property, so that aspirin is now being widely used to treat cardiovascular complications.¹

Although gas and liquid chromatographic methods are the most specific methods for salicylate^{2,3}, but their general availability, especially for emergency use, is limited and probably not necessary.^{4,5} Official methods, namely those proposed by the British Pharmacopoeia⁶, are usually based on time-consuming and tedious titrimetric procedures, which in themselves, justify the search for speedier methods. Direct potentiometric methods, however, are simpler and faster. In this context, the construction and analytical applications of electrodes that are sensitive to salicylate ion have been described.

Most salicylate ion-sensitive electrodes use a liquid sensor immobilized in a porous membrane of Orion electrode series 92-20.⁷⁻¹⁴ This fact restrains its utilization due to manipulation difficulty and the mechanical deficiency of this kind of setting up. With the evolution of ion-selective electrodes, in its brief history and development, other kinds of salicylate ion-sensitive electrodes has been described in the literature.¹⁵⁻²⁶

This paper describes for the first time the behavior

and use of an electrode of the second kind, Pt[Hg]Hg₂(Salic)₂, the sensor of which was immobilized in graphite. This electrode works according to a principle which is quite different from that associated with previously described electrodes. The experimental variables that contribute to this electrode response, the calculation procedures utilized to determine the calibration curves jointly with the evaluation of this performance for the assay of aspirin in tablets (after hydrolysis of acetylsalicylate acid to salicylate), are described.

Experimental

Materials and solutions

Distilled, deionized water and “grade A” glassware were used throughout. All of the chemicals employed were of analytical reagent grade. Carbonate-free sodium hydroxide solutions were standardized potentiometrically with acid potassium phthalate, and then stored in polyethylene bottles protected with soda-lime tubes. The perchloric acid solutions were standardized potentiometrically with standard sodium hydroxide solutions. A sodium salicylate stock solution was standardized potentiometrically with a standard perchloric acid solution. Stock solutions of sodium perchlorate were analyzed by evaporating and drying to constant mass at 120°C.

Mercurous salicylate was prepared by mixing, in aqueous solution, the corresponding nitrate with an excess of sodium salicylate. The resulting precipitate was filtered through a sintered glass funnel, washed

[†] To whom correspondence should be addressed.

with deionized water until nitrate free, and then dried in a desiccator over calcium chloride, under reduced pressure, at room temperature, to constant mass. A white powder was obtained as the final product.

Metallic mercury was treated sequentially with 5%(v/v) nitric acid, deionized water, 3%(m/v) sodium hydroxide, deionized water, 3%(v/v) nitric acid and deionized water. After being dried with a filter paper it was distilled by following the conventional procedure.

The mercurous salicylate indicator electrode was prepared as follows: mercurous salicylate (600 mg) and metallic mercury (200 mg) were mixed in an agate mortar and the material was crushed until a homogeneous solid was obtained. Pure powdered graphite (190 mg) was then added and the crushing process was continued until perfect homogenization was attained. Part of the resulting solid was transferred to a press mold, being compressed at 20000 psi, for about 300 s. The black pellet (1.5 mm thickness, 13 mm o.d. and 600 mg mass) was fixed at one end of a glass tube (13 mm o.d., 80 mm length) with a silicone-rubber glue ("Rhodiastic", Rhône-Poulenc, France) and allowed to dry for 48 h. Sufficient metallic mercury was then introduced into the tube to produce a small pool upon the inner pellet surface; electrical contact was established through a platinum wire plunged into the mercury pool and a subsequent conductor cable. The resulting electrode is schematized in Fig. 1.

Instruments

The electromotive force (emf) values are read to the nearest 0.1 mV with a "Metrohm" Model 670 Titroprocessor. The reference electrode was a "Metrohm" Ag|AgCl double junction, Model 6.0726.100. The pH of the solutions was adjusted with a "Metrohm" combination pH electrode (Model 6.0234.100). A thermostated titration cell ($25.0 \pm 0.1^\circ\text{C}$) was employed. Volume measurements (± 0.001 ml) were performed with "Metrohm" Model 665 automatic burettes. All experiments were performed in a thermostated room ($25 \pm 1^\circ\text{C}$).

Potentiometric cell

The cell shown below was used; where Salic stands for salicylate ion and x was in the range $(0.06 - 10.0) \times 10^{-2}$ mol/l. The ionic strength (I) of cell compartments was kept constant over the range 0.5 - 3.0 mol/l by adding sodium perchlorate. No flow of chloride ions from the reference electrode into the test solution could be detected during the measurements.

Electrodes conditioning

The Pt|Hg|Hg₂(Salic)₂|Graphite indicator electrode

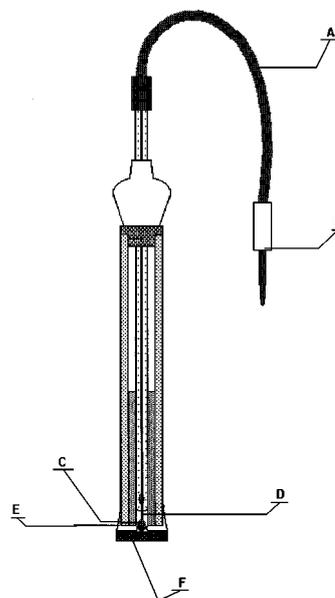


Fig. 1 Mercury(I) salicylate electrode. A, conductor cable; B, banana plug; C, metallic mercury; D, Pt wire; E, silicone glue; F, sensor pellet (Graphite|Hg₂(Salic)₂|Hg).

was immersed in a small amount of sodium salicylate solution (0.100 mol/l) at an appropriate ionic strength, and adjusted with a sodium perchlorate solution. The external surface of the indicator electrode sensitive pellet was restored by polishing with in a sheet of paper, washed and drier in absorbent paper, before the realization of each experiment.

The Ag|AgCl reference electrode with a double liquid junction was filled in a sodium chloride solution (0.010 mol/l), the ionic strength of which had been previously adjusted with a sodium perchlorate solution and the vertical saline bridge was filled in a sodium perchlorate solution at the same ionic strength.

Calibration curves (calculation procedure)

The emf of cell (a) may be defined by^{27,28}

$$E = (E'_{\text{salic}})_o - S \log a_{\text{salic}} + E_j \quad (1)$$

where

$a_{\text{salic}} = y_{\text{salic}} \cdot [\text{Salic}] = \text{activity of salicylate ion (mol/l)}$

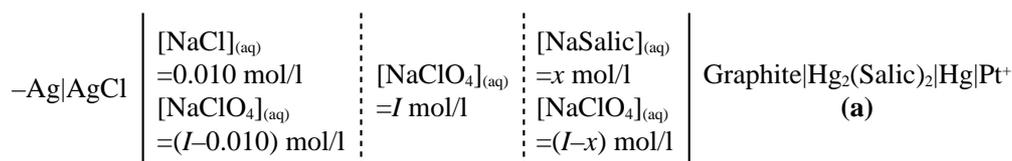
$y_{\text{salic}} = \text{activity coefficient of salicylate ion (molar scale)}$

$[\text{Salic}] = \text{concentration of salicylate ion}$

$S = \text{slope of calibration curve (Nernst coefficient} = 2.303RT/nF = 59.16 \text{ mV, at } 25^\circ\text{C)}$

$(E'_{\text{salic}})_o = E_{\text{Hg|Hg}_2(\text{Salic})_2}^o - E_{\text{ref}}$

$E_{\text{Hg|Hg}_2(\text{Salic})_2}^o = \text{standard potential of indicator electrode}$



E_{ref} =potential of reference electrode

E_j =liquid junction potential (mV)

Equation (1) can be rearranged as:

$$E = (E'_{\text{salic}})_o - S \log y_{\text{salic}} - S \log [\text{Salic}] + E_j \quad (2)$$

For this particular case, the experimental conditions are arranged such that E_j varies less than the precision of the measurement.^{27,29} If it is considered (for each constant I value) that

$$E'_{\text{salic}} = (E'_{\text{salic}})_o - S \log y_{\text{salic}} = \text{constant}^{27,28,30} \quad (3)$$

we have

$$E = E'_{\text{salic}} - S \log [\text{Salic}] \quad (4)$$

where E'_{salic} =formal potential cell.

From sufficient experimental (E , $[\text{Salic}]$) pairs of values, we can determine the E'_{salic} and S parameters (corresponding to the fixed I value) using the linear regression method.²⁷ The parameters E'_{salic} and S for the salicylate electrode are given in Table 1.

Determination of salicylate in aspirin tablets

Samples of three different brands (Aspirin[®], AAS[®] and Melhoral[®]) were finely powdered. A portion of the powder, equivalent to 400 mg of acetylsalicylic acid, was heated under reflux with 25 ml of sodium hydroxide (0.5 mol/l) for fifteen minutes. In the sequence this solution, whose pH was adjusted to 6.0 with perchloric acid, was then filtered and made up to 250 ml in a volumetric flask. An aliquot (25 ml) of the solution was employed for salicylate determination by using the salicylate sensitive electrode. A standard additions method was employed to evaluate the concentration of salicylate. A standard procedure for the assay of soluble aspirin tablets was used as the reference method.⁶

Results and Discussion

Effect of the ionic strength on the calibration parameters

The variation of E'_{salic} (Table 1) reflects the well-known dependence of the single-ion activity coefficients on the ionic strength. At present, there are no plausible reasons to explain the variations in S with the ionic strength (Table 1). Investigations on the subject have been scant in the literature; either values are not given³¹ or only mean values are provided.³² Previous work from this laboratory²⁷ shows that variation occurs randomly for well-established ion-selective electrodes (*i.e.*, glass, copper, cadmium and lead), just as found for the salicylate electrode described in the present work, *i.e.*, no definite trend can be detected. The same behavior was observed for data gathered recently in this laboratory with the fluoride electrode ("Orion", Model 94-04). In this case, S values of 59.8, 57.8, 61.1, 58.0,

Table 1 Experimental parameters for the salicylate electrode, in several ionic strengths, pH 6.0 and temperature of (25.0±0.1)°C

$I/\text{mol l}^{-1a}$	$E'_{\text{Salic}}/\text{mV}^b$	$S_{\text{exp}}/(\text{mV}/\text{dec})^b$	r^c
0.500	114.6	59.92	0.9974
0.700	116.2	58.79	0.9966
0.900	117.3	56.45	0.9968
1.200	119.1	56.77	0.9976
1.500	121.8	59.29	0.9964
1.800	123.3	56.03	0.9983
2.100	125.2	62.35	0.99556
2.400	127.2	59.86	0.9947
2.700	129.3	59.02	0.9956
3.000	131.7	58.12	0.9945

a. I adjusted with NaClO_4 .

b. Calculated values from Eq.(4), considering E_j negligible.

c. Correlation coefficient.

61.4, 59.8, 60.3 and 59.8 mV/dec, were determined for ionic strengths of 0.1, 0.3, 0.5, 1.0, 1.5, 2.0, 2.5 and 3.0 mol/l, respectively. It is felt that considerable development is required before a reasonable explanation can be obtained. For the present analytical purpose, the ionic strength was conveniently fixed at 0.500 mol/l.

Effect of the pH

The pH dependence of the electrode potential was tested over the pH range of 6.0 – 8.0 for 1.00×10^{-1} , 1.00×10^{-2} and 1.00×10^{-3} mol/l salicylate ion. The pH was adjusted with a perchloric or sodium hydroxide solution. The potentials were independent of the pH in the range 6.0 – 8.0; this can be taken as the working pH range of the electrode.

Interference study

The influence of 10 different organic and inorganic anions (lactate, acetate, propionate, formate, nitrate, sulfate, chloride, bromide, iodide and perchlorate) on electrode response was investigated. The study was made at a 10^{-2} mol/l concentration of both salicylate and the interfering species. The organic acid anions have no significant effect (*i.e.*, less than 5%) on the response of the salicylate electrode. No interference at all is caused by nitrate, sulfate and perchlorate.

The anions Cl^- , Br^- and I^- interfere seriously, resulting in a deposit of the respective mercury(I) salt on the electrode surface. Removal of this interfering film (by scrubbing or by polishing the electrode surface) is thus required for restoring the electrode activity. However, these anions are seldom found in aspirin tablets, and hence the proposed electrode can generally be used for the determination of aspirin (after hydrolysis of acetylsalicylic acid to salicylate) in tablet formulations.

The response mechanism of the present salicylate electrode is the same as that of a second kind electrode, such as the silver-silver chloride electrode. Thus, the selectivity coefficient of the present electrode (k') is

expected to be determined, at least approximately, by the ratio of the solubility product (K_{ps}) of $Hg_2(Salic)_2$ to that of Hg_2L_n (L =organic or inorganic interfering species).³³⁻³⁶ However, the k' values could not be determined in the present study, since the solubility product of $Hg_2(Salic)_2$ has not yet been assigned in the literature.

Determination of the response time and calibration curves of the salicylate sensitive electrode

The response time of the indicator electrode was determined by measuring the cell electromotive force every 30 s, from 0 until 300 s, for each value of sodium salicylate concentration previously established, at an ionic strength of 0.500 mol/l. These measurements permitted us to verify that, after 30 s, the potential value of the cell was kept practically stable for each concentration of the analyte studied. In this way, the response time for the indicator electrode was fixed at 30 s to carry out all of the experiments using other ionic strengths.

The calibration curves (for each constant I value) were obtained by the successive addition of small volumes (0.250 ml) of a standardized solution of sodium salicylate (pH 6.0), in an ionic strength adjusted with sodium perchlorate (pH 6.0) to a potentiometric cell made of glass (thermostatized at $25.0 \pm 0.1^\circ C$) with double walls (Metrohm, number 6.1418.220), containing 25.000 ml of sodium perchlorate (pH 6.0) and 0.100 ml of sodium salicylate 0.150 mol/l (pH 6.0), both with the same ionic strength as the solution added. After each addition under continuous agitation, the emf of cell (a) was measured. A small amount of sodium salicylate was initially added (0.100 ml, 0.150 mol/l) to provide better reading stability and a faster response time.

Characteristics of the electrode

The results show that the graphite behaves as an inert substance and conductor in the immobilization process of the sensor of the electrode. The electrode is easily constructed, it shows a service life superior to 18 months, is low in cost, has a fast response time (inferior to 30 s) and the slopes of its calibration curves agree with the Nernst coefficient in an interval of salicylate concentration range 6.0×10^{-4} and 1.0×10^{-1} mol/l, at pH 6.0, with an average slope of -58.66 mV, per unit change of $p[Salic](T=25^\circ C)$ at $I=0.500 - 3.00$ mol/l.

An advantage of this electrode is that the anion ClO_4^- , different from what it is observed for the salicylate-sensitive liquid-membrane electrodes^{13,14,26} does not interfere in its response. In quantitative studies about equilibria in solution, it is utilized an excess of inert electrolyte, so that the ionic strength of the solution is kept effectively constant during all the time encompassed by the experiments.²⁷⁻³⁰

Among the reduced number of electrolytes suited for that purpose, sodium perchlorate is by far the most frequently used.³⁷ The results obtained in this work show that the electrode mentioned above can be utilized to determine the concentration of free salicylate ions in a

Table 2 Comparison of some salicylate sensitive electrodes

Type of electrode	Slope (mV/dec)	Linear response/mol l ⁻¹	Lifetime
Electrode described in this work	-58.66^a	6.0×10^{-4} to 1.0×10^{-1}	>18 months
Conductor glass ²⁰	-55.8	10^{-4} to 10^{-1}	6 months
Coated wire ⁹	-53.0	10^{-3} to 10^{-1}	3 weeks
Liquid membrane ¹³	-59.0	10^{-5} to 10^{-1}	not reported
Liquid membrane ¹⁴	-56.0	10^{-4} to 10^{-1}	4 weeks
PVC membrane ¹²	-59.0	10^{-3} to 10^{-1}	not reported
PVC membrane ¹⁵	-56.0	10^{-4} to 10^{-1}	200 measures
PVC membrane ¹⁶	-36.0	10^{-4} to 10^{-1}	not reported
PVC membrane ¹⁹	-(55 to 60)	10^{-4} to 10^{-2}	not reported
PVC membrane ²¹	-58.0	10^{-3} to 10^{-1}	2 weeks ^b
PVC membrane ²³	-(50 to 54)	10^{-5} to 10^{-1}	not reported
PVC membrane ²⁶	-(60 \pm 2)	(6 \pm 2)·10 ^{-4c}	not reported

a. Average value of S , referred to the ionic strength range studied.

b. Lifetime studies of over two weeks have not been done.

c. Detection limit.

constant ionic strength, adjusted with sodium perchlorate. Therefore, the stability constants for metallic ion complexes with salicylate can be calculated.³⁸

Based on the results shown in Table 2, we can verify that the most important characteristics of the electrode developed in this laboratory are similar or superior (especially the lifetime) to the other salicylate electrodes described in the literature.

Analytical applications

The electrode has been advantageously employed to the determination of salicylate in three different drugs (Aspirin[®], AAS[®] and Melhoral[®]). Salicylate present in pharmaceutical preparations was determined as described in the experimental section. Table 3 gives the results of the aspirin analysis in tablet formulations. According to the results listed in Table 3, a good correlation between the electrode method and pharmacopoeial method⁶ is verified.

It is worth noting that carboxylates are the largest single class of complexing donor groups in the environment and are present as a result of either degradative processes involving naturally-occurring bioorganic substances or through biological and chemical oxidations of terminal groups of hydrocarbon derivatives.³⁹ From an analytical point of view, the development of carboxylate sensitive electrodes assume a great significance due to the fact that many materials of clinical, biochemical, pharmacological and nutritional importance include carboxylate groups. Work in this area and the development of electrodes sensitive to other carboxylates forming low-solubility precipitates with mercurous ion is presently proceeding.

In summary, the mercury-mercurous salicylate electrode shows good working characteristics, the most noteworthy of which are long lifetimes, low cost, stability and repeatability. The electrode is useful for sali-

Table 3 Results of determination of aspirin in tablets obtained by the salicylate sensitive electrode compared with those obtained by BP method⁶

Brand (supplier)	Nominal/ mg	Recovery, % ^a	
		Electrode method ^b	BP method
Aspirin [®] (Bayer S.A., Brazil)	500.0	101.2±1.2	101.0±1.4
AAS [®] (Sanofi Winthrop, Brazil)	500.0	101.3±0.5	101.1±0.6
Melhoral [®] (Sanofi Winthrop, Brazil)	500.0	101.3±1.4	101.9±0.5

a. Average±s.d. for three separate determinations; assay as a % of the label claim.

b. The experimental parameters (E_{Salic}° , S) employed in determination of aspirin by using the electrode method was obtained in $I=0.500$ mol/l, pH 6.0 and temperature of $(25.0\pm 0.1)^{\circ}\text{C}$.

ylate determinations in some commercial aspirin tablets. The method has the advantage of simplicity and speed compared to standard procedures.

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