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A new salicylate ISFET for the determination of salicylic and acetylsalicylic acid in drugs*

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Abstract: A salicylate ISFET for the analysis of salicylic and acetylsalicylic acid in drugs is described. It is based on a salicylate ion selective membrane coated on the surface of the Si_3N_4 gate of the FET. The sensitive membrane consists of tetra-dodecylammonium salicylate, polyvinyl chloride and a proper plasticizer. The linearity range of the sensor is 5×10^{-5}–1.5×10^{-2} M for the salicylic acid, and 7×10^{-5}–1.5×10^{-2} M for the acetylsalicylic acid, respectively. The detection limit for the two compounds is 5×10^{-5} M while the response time is ≤20 s. The effect of pH and different interfering ions was also studied. The sensor was used to analyse the content of acetylsalicylic and salicylic acid in some drugs, and the accuracy of the method was evaluated through recovery tests. The results obtained with this method are well correlated either with those obtained with a classical ISE employing the same sensitive membrane or with the classical volumetric method.

Keywords: *Salicylic and acetylsalicylic acid; analysis; salicylate ISFET.*

Introduction

Salicylate is one of the most important active principles of many pharmaceutical products as well as several of its derivatives. In fact, several common pharmaceutical formulations contain acetylsalicylic acid (e.g. aspirin), salicylic acid, methyl salicylate and salsalate.

Salicylic acid is mainly used as external therapeutical agent (keratolytic agent), for instance it can be used to remove warts, hard corns and callouses [1]. On the other hand, despite the introduction of several new drugs, acetylsalicylic acid is still the most widely prescribed analgesic-antipyretic and anti-inflammatory agent. According to some estimates, the amount of this drug, consumed only in the United States, is higher than 10–20 $\times 10^3$ tons per year [2]. Although the efficacy and safety of acetylsalicylic acid as analgesic and antirheumatic agent is well known, it is necessary to be aware of its role in Reye's syndrome and as a common cause of lethal drug poisoning in young children, as well as its potential for serious toxicity if used improperly. Therefore, the analysis of acetylsalicylic acid has become a routine assay in clinical chemistry and in the quality control of drug production,

For the above reasons, though a reference volumetric method is reported by the British Pharmacopoeia [3] the development and improvement of other methods of analysis for these compounds has continued. Several methods have been proposed, based on spectroscopic techniques [4–9], high-performance liquid chromatography [10–13], fluorescence immunoassay [14] and several electrochemical techniques, in particular amperometric enzyme sensors [15–17], ISEs (ion selective electrode) [18] and optical sensors [19], etc. However the use of salicylate ISFETs (ion sensitive field effect transistor) for the analysis of acetylsalicylic acid and salicylic acid has not yet been reported.

In this paper, a new salicylate ISFET based on a polymeric salicylate ion sensitive membrane coated on the surface of the Si_3N_4 gate of a FET was prepared. The sensitive membrane consisted of poly(vinyl-chloride), a proper plasticizer and a new exchanger, the tetra-dodecylammonium salicylate (TDDAS), which

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is different from other exchangers previously used to fabricate salicylate ISEs [18]. The sensor response to both salicylate and acetylsalicylate and analytical properties were studied. In addition, the new probe has been used to determine the content of acetylsalicylic acid and salicylic acid in some drugs, which include intestine-soluble tablets containing acetylsalicylic acid and ointments containing salicylic acid. The accuracy of the method was evaluated by means of recovery tests. The results were compared with those obtained with the classical volumetric method and with those found using an ISE based on the same sensitive membrane.

Experimental

Chemicals

Acetylsalicylic acid and salicylic acid were supplied by the Sigma Chemical Co. (St Louis, MO, USA). Polyvinyl-chloride (PVC, high molecular mass), dioctylphthalate (DOP) and bis(2-ethyl-hexyl)sebacate (BEES) were purchased from Fluka (Buchs, Switzerland). The dibutylphthalate (DBP) was supplied by Merck (Darmstadt, Germany). The tetradodecylammonium iodide (TDDAI, 98% purity), employed to prepare the new exchanger i.e. tetradodecylammonium salicylate (TDDAS), has been synthesized at the Institute of Organic Chemistry, Academia Sinica (Shanghai, China) [20]. All other reagents, of analytical reagent grade and used without further purification, were supplied by Farmitalia Carlo Erba (Milan, Italy).

Samples

The percentage composition of the analysed samples, three commercial formulations and one galenic ointment, is shown in Table 1.

Apparatus and measurements

Potentiometric measurements with classical ISE were carried out using a digital pH meter (Orion model 720, Orion Co., MA, USA).

Output voltage measurements with salicylate ISFET were carried out using an apparatus designed and assembled in our laboratory for measurements by CHEMFET (chemical field effect transistor) devices [21]. The instrument operates at constant drain current, (100 μA) and the design of the instrument is based on the feedback compensation principle and has been thoroughly described in the paper mentioned above [21]. The FET was supplied by the Institute of Electronics, Academia Sinica (Beijing, China).

Measurements were performed in a glass cell with a 35 ml volume using a saturated calomel electrode as reference electrode. The temperature of the test solution was kept at 20 ± 1°C by using a thermostatted water jacket. The following elemental measurement cells were used for the ISFET (I) and for the classical ISE (II), respectively.

Table 1
Composition of the pharmaceutical formulations analysed. Nominal values as supplied by manufacturing firms

Drug no. and its pharmaceutical form	Component	Content (as % w/w)
1 (Tablet)	Acetylsalicylic acid	12.5
	Ascorbic acid (vitamin C)	7.5
	Monosodium citrate	37.5
	Sodium bicarbonate	28.4
	Sodium carbonate	6.2
	Citric acid	7.5
2 (Enteric-coated tablet)	Acetylsalicylic acid	79.3
	Corn starch	19.7
	Colloidal silica	1.0
3 (Commercial ointment)	Salicylic acid	25.0
	Vaseline	58.0
	Talc	15.0
	Monosodium citrate	1.8
	Perfumer	0.2
4 (Galenic ointment)	Salicylic acid	19.2
	Vaseline	30.0
	Sodium carbonate	22.3
	Sodium bicarbonate	11.5
	Monosodium citrate	16.9

Hg/Hg_2Cl_2, KCl(st)//Test solution/Polymeric membrane/Gate-FET (1)

Hg/Hg_2Cl_2, KCl(st)//Test solution/Polymeric membrane/Inner solution, Ag/AgCl. (2)

Exchanger preparation

The new exchanger TDDAS was prepared following a procedure similar to that described in a recent paper [22]. Such procedure can be briefly described as follows: 0.5 g TDDAI was dissolved in 15 ml of chloroform. The organic phase was partitioned with 60 ml of an aqueous solution of sodium salicylate (0.01 M pH 9.0) and the two phases were separated.

This procedure was repeated several times, until no iodide ions were found in the aqueous phase. The organic phase was then washed with distilled water four times. The organic phase was evaporated, at room temperature, and TDDAS was obtained as residue.

ISFET and classical ISE preparation

Salicylate sensitive polymeric membranes were prepared by the following procedure: 50 mg of TDDAS, 0.81 g of plasticizer (DBP) and 0.38 g of PVC were dissolved in 10 ml of (tetrahydrofuran (THF). After stirring, a clear solution was obtained, which was poured into a Petri dish (48 mm, i.d.). After the THF was evaporated at room temperature, a membrane with 0.3 mm thickness was obtained. A disc with a proper diameter was cut from the membrane with a hand-punch. When the classical ISE was constructed, the disk was glued to the bottom of the electrode body (PVC tubing, 10 mm o.d.) employing a 6% (w/w) THF solution of PVC. The inner reference electrode was an Ag/AgCl electrode and the inner solution was 0.01 M KCl and 0.01 M sodium salicylate. When the salicylate ISFET was fabricated, a drop of the above described THF solution, containing PVC, TDDAS and DBP, was deposited on the surface of the FET. After THF evaporation, at room temperature, the "gate" of the FET is coated with the polymeric salicylate sensitive membrane. It should be pointed out that the inner surface of the membrane must be closely in contact with the outer surface of the FET "gate" to avoid the formation of any air bubble between the two surfaces.

The total area of every chip is (1.4 × 2.4) mm^2. After washing with isopropanol, the chip was mounted on a plastic stick made by an epoxy resin–glass fibre and connected to the electrical measurement system by using an ultrasonic wire-bounder (Model 501, Zhenjang, Jangsu, China); all other parts were encapsulated using an epoxy resin (EPOXY 618, Shanghai Resin Factory, Shanghai,

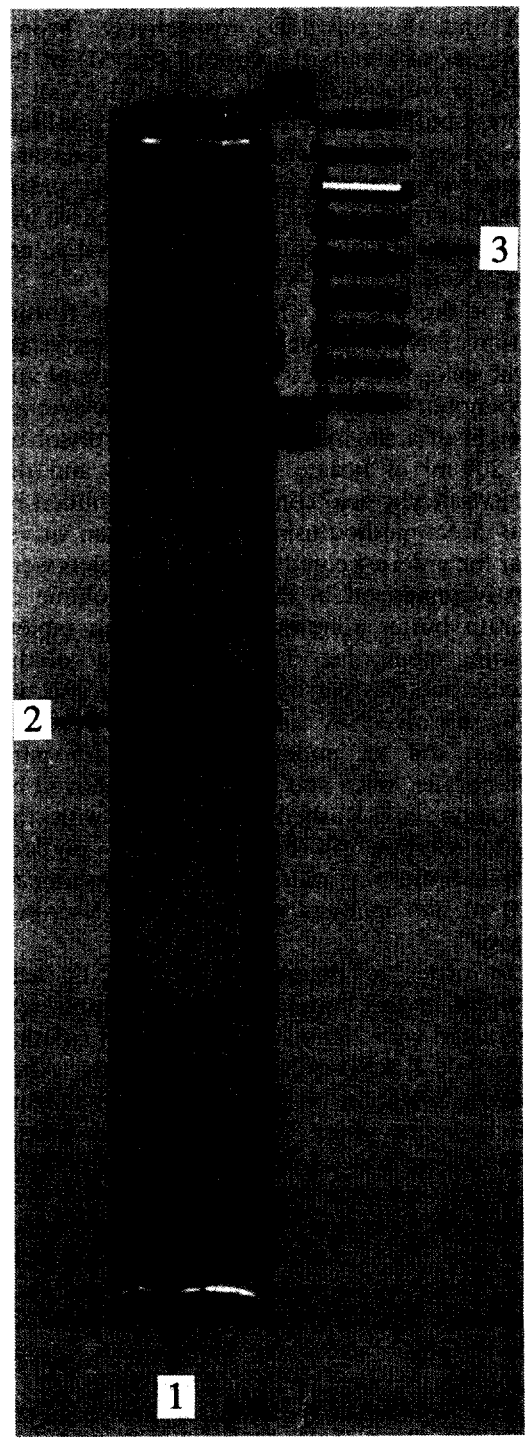

Figure 1
Photograph of the probe: (1) ISFET; (2) stick; (3) electrical connections.

China), except the working region of the chip. The ISFET fixed on the stick and the electrical connections are shown in Fig. 1.

Assay

Calibration curves for salicylic and acetylsalicylic acids were obtained by using the cell (I) and the cell (II), respectively. Proper volumes of standard solutions (0.1 M) of the analyte were successively added to 25 ml of borate buffer solution and after each addition, the potential value was recorded. All measurements were carried out under stirring and at constant temperature. A calibration curve was then obtained by plotting the potential values (mV) vs log$C$ (C in M).

For the analysis of pharmaceutical formulations (sold as tablets) containing acetylsalicylic acid, five tablets were finely ground and an amount of powder equivalent to the average weight of a single tablet (3.2 g) was dissolved in 200 ml of borate buffer (pH 9) and the acetylsalicylic acid content was determined by the direct method using the calibration curve. For the enteric-coated tablets, five tablets were firstly immersed in the minimum volume of borate buffer solution to soften the tablets coating membrane. Then, the surface of the membrane was cut by using a lancet and the drug dissolved by adding 100 ml of borate buffer and let under stirring for 15 min. Membrane, silica and starch were removed by filtration and washed three times with the buffer solution. All the solutions were pooled, borate buffer was added up to a final volume of 200 ml and analysis performed as described above.

In order to determine the salicylic acid content in the ointments, 1 g of sample was extracted with 200 ml of a hot NaOH solution (pH 9.0, T = 70–80°C), under stirring. After cooling down, the oil phase was separated from the aqueous phase. Of the aqueous phase, 100 ml were added with 400 ml of borate buffer (pH 9.0) and the salicylic acid content was determined using the calibration curve method. The treatment and the dilution of pharmaceutical samples employed was such that the final concentration of salicylic or acetylsalicylic acid to be determined, falls in the linearity range of the calibration graph.

The volumetric analysis of acetylsalicylic acid was performed as follows: 1 g of sample was dissolved in 10 ml of ethanol (95%), add 50 ml of 0.5 M sodium hydroxide VS were added, and the flask was closed and allowed to stand for 1 h. Then 0.2 ml of phenolphtalein solution were added and titration carried out with 0.5 M hydrochloric acid VS. The operations were repeated in an identical solution not containing the substance to be determined. The difference between the titrations represents the amount of sodium hydroxide required for the analysis. Each ml of 0.5 M sodium hydroxide VS is equivalent to 45 mg of acetylsalicylic acid.

The volumetric analysis of salicylic acid was performed as follows: 0.5 g of sample were dissolved in 200 ml of water and titrate with 0.1 M sodium hydroxide VS, using phenol red solution as indicator, until reddish violet colour was obtained. Each ml of 0.1 M sodium hydroxide VS is equivalent to 13.8 mg of salicylic acid.

Results

Figure 2 shows the trend of the sensitivity (as slope of the calibration curve) with pH for salicylate ISFET and classical ISE. It can be noted that the sensor has a wide operative pH range. In the range of pH 6.9–12.7, no remarkable changes on the response, slope and linearity range of the sensor were found.

A complete characterization of the salicylate ISFET, in the analysis of salicylic, or acetylsalicylic acid, was carried out; the working conditions are reported in Table 2 while the main analytical data are summarized in Table 3; in both tables, the data are compared with those obtained using the classical ISE. In Table 4 the main parameters of the calibration curve, obtained for the salicylate ISFET, are reported

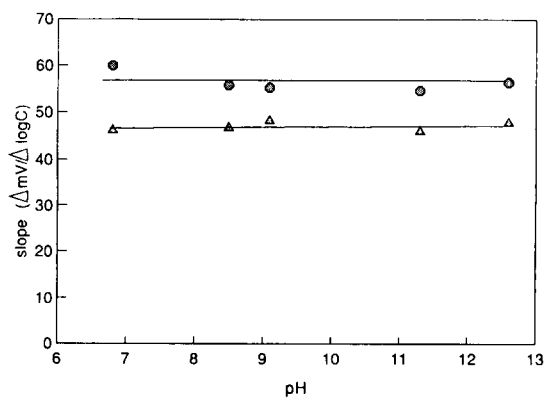

Figure 2
Behaviour of the slope of the calibration curve of acetylsalicylate with pH, for salicylate ISFET (▲) and classical ISE (●).

Table 2
Optimized working conditions for salicylate ISFET and classical salicylate ISE for the analysis of salicylate and acetylsalicylate

	ISFET	ISE
Working electrode	Polymeric membrane ISFET	Classical polymeric membrane ISE
Inner solution	—	0.01 M KCl; 0.01 M salicylate
Reference electrode	Saturated calomel	Saturated calomel
Polymeric coated membrane	PVC containing plasticizer and exchanger	PVC containing plasticizer and exchanger
Exchanger	Tetradodecylammonium salicylate (TDDAS)	Tetradodecylammonium salicylate (TDDAS)
Plasticizer	Dibutylphthalate (DBP)	Dibutylphthalate (DBP)
Buffer	0.01 M borate	0.01 M borate
pH	9.0	9.0
Temperature	20°C	20°C

Table 3
Main analytical data* of salicylate ISFET and classical salicylate ISE in salicylate and acetylsalicylate analysis

	Salicylate analysis		Acetylsalicylate analysis	
	ISFET	ISE	ISFET	ISE
Lifetime (days)	≥30	≥180	≥30	≥180
Response time(s)	15	30	20	40
Linearity range (M)	5.0×10^{-5}–1.5×10^{-2}	5.0×10^{-5}–1.5×10^{-2}	7.0×10^{-5}–1.5×10^{-2}	5.0×10^{-5}–1.5×10^{-2}
Minimum detection limit (M)	3.0×10^{-5}	3.0×10^{-5}	5.0×10^{-5}	3.0×10^{-5}
Slope (ΔmV/Δlog$C$) of the calibration curve (C = mM)	49.1 (±0.2)	−58.2 (±0.01)	47.1 (±0.2)	−58.2 (±0.06)
Correlation coefficient, r	0.9991	−0.9999	0.9990	−0.9997
Precision on standard solutions (Pooled SD%)	1.8	1.8	0.7	3.7
Inaccuracy on standard solutions (% values)	−6.4–+4.5	−4.9–+1.7	−8.2–+6.8	−4.3–+7.0
Precision on drugs (RSD%)	≤6.3	≤6.3	≤7.1	≤2.3
Inaccuracy on drugs (by standard addition method)	−4.7–+0.6	−1.0–+0.2	−2.8–−1.7	−3.5–−1.2

*Data concerning the calibration graph, the linearity range, the correlation coefficient and the limit of detection were obtained from the experimental values (mV vs log$C$) processed using an HP86 PC and a home-made program described in detail elsewhere [32].

Table 4
Effect of the plasticizer on the calibration curve parameters of salicylate obtained with the salicylate ISFET. Response to salicylate

Plasticizer	Linearity range (M)	Slope (ΔmV/Δlog*C*)	Correlation coefficient *r*
DBP	5×10^{-5}–1.5×10^{-2}	49.1 (SD = ±0.2)	0.9991
BEES	5×10^{-5}–1.5×10^{-2}	45.1 (SD = ±0.2)	0.9991
DOP	1×10^{-4}–2×10^{-3}	43.7 (SD = ±1.5)	0.9987

Table 5
Effect of the plasticizer on the selectivity coefficients of the salicylate ISFET, obtained by the "mixed solutions method" [23]

Interferent, *j*		K_{ij} Plasticizer		
Type	Background level (M)	DBP	BEES	DOP
SO_4^{2-}	1×10^{-1}	1×10^{-5}	1×10^{-5}	1×10^{-5}
NO_3^-	1×10^{-2}	3×10^{-2}	5×10^{-2}	5×10^{-2}
Cl^-	1×10^{-2}	1×10^{-4}	1×10^{-4}	2×10^{-4}
CO_3^{2-}	1×10^{-2}	1×10^{-3}	1×10^{-3}	1×10^{-3}
HCO_3^-	1×10^{-2}	1×10^{-4}	1×10^{-4}	1×10^{-4}
OH^-	5×10^{-2}	2×10^{-4}	2×10^{-4}	2×10^{-4}
Phosphate	2.5×10^{-2}	1×10^{-5}	1×10^{-5}	1×10^{-5}
Citrate	1×10^{-2}	1×10^{-5}	1×10^{-5}	1×10^{-5}
Antipyrine	1×10^{-2}	1×10^{-5}	1×10^{-5}	1×10^{-5}
Phthalate	1×10^{-2}	1×10^{-2}	1×10^{-2}	5×10^{-2}
Benzoate	1×10^{-2}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Penicillin G	1×10^{-2}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Piperacillin	1×10^{-2}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Methicillin	1×10^{-2}	5×10^{-5}	1×10^{-4}	1×10^{-4}
Nicotinic acid	1×10^{-2}	1×10^{-4}	1×10^{-4}	1×10^{-4}
Ascorbic acid	1×10^{-2}	2×10^{-4}	2×10^{-4}	5×10^{-4}
Propylphenazon*	1×10^{-2}	5×10^{-5}	—	—
Codein phosphate*	1×10^{-2}	1×10^{-4}	—	—

*Obtained by the "separate solutions method" [23].

as a function of the type of plasticizer employed for the preparation of the membrane. The potentiometric selectivity coefficients, determined by means of the mixed solution method [23], for membranes containing different plasticizers, are reported in Table 5. The data indicate that the plasticizer has a certain effect on the response of the salicylate ISFET and that among the three plasticizers, DBP can be considered the best one.

Table 6 gives the results and the repeatability data obtained for the analysis of authentic matrices (tablets containing acetylsalicylic acid and ointment containing salicylic acid) together with the nominal values supplied by the manufacturers.

Table 7 reports the recovery data for tablets and ointments analysis by the standard addition method obtained using both the ISFET and classical ISE.

Finally a comparison of some results obtained by salicylate ISFET, classical ISE and volumetric method, is shown in Table 8.

Discussion

It can be observed that the data in Table 2 have been found by working at pH 9.0 obtained by borate buffer. Indeed, the stability of acetylsalicylic acid in solid dosage form is satisfactory if contact with water is avoided, since this substance can easily hydrolyse to salicylic acid and acetic acid [24]. The rate of hydrolysis depends on the pH and it increases for pH values lower than 2 or higher than 8 [1]. On the other hand, Fig. 2 shows that both the salicylate ISFET and classical ISE can be used in wide pH range (about 7–12) without significant response variations. Therefore, it can be safely assumed that at pH 9 the content of acetylsalicylic acid corresponds to the salicylic acid produced by the fast hydrolysis reaction, while, at the same time, the possible interference caused by the OH^- ions that should occur at higher pH values, is avoided.

The main analytical data obtained with standard solutions of salicylic acid, acetylsali-

Table 6
Analysis of acetylsalicylic and salicylic acid in drugs by salicylate ISFET and comparison with nominal values

Drug no. and its pharmaceutical form	Nominal value (% w/w) (*a*)	Found value (% w/w)	Mean found value (% w/w) (*b*)	RSD%	$\frac{b-a}{a}$ %
Acetylsalicylic acid					
1 (Tablet)	12.5	12.6 12.3 12.0 12.3 12.6	12.4	1.8	−0.8
2 (enteric-coated tablet)	79.3	77.5 80.6 76.3 79.1 77.8	78.3	1.9	−1.3
Salicylic acid					
3 (Commercial ointment)	25.0	21.4 20.9 24.6 22.4 24.0	22.7	7.1	−9.2
4 (Galenic ointment)	19.2	18.5 18.1 17.6 18.9 18.3	18.3	2.4	−4.7

cylic acid or with authentic samples are similar using the two sensors (Table 3). However, the ISFET device shows always a faster response than the ISE, while the slope of the ISE calibration curve is closer to the Nernstian value.

Different plasticizers can be used in the preparation of the polymeric membrane. Table 4 shows that the membranes containing dibutylphthalate exhibit a slope of the calibration curve closer to the theoretical value, while the sensor response time is not affected by the type of plasticizer used.

The selectivity coefficients reported in Table 5 show that the interference due to most of the organic and inorganic anions examined is very low. Only phthalate and nitrate seem to exhibit a certain interfering effect. It should be pointed out that the selectivity coefficient of substances such as ascorbic acid, codeine phosphate, propylphenazone, citrate, carbonate and bicarbonate is very low. Therefore, the direct determination of acetylsalicylic acid and salicylic acid, in pharmaceutical commercial formulations, where the aforementioned substances are commonly contained (see Table 1), can be performed. Further, Tables 6 and 7 show that such direct determination in authentic samples can be carried out with a good precision and accuracy.

Finally, Table 8 shows that the data obtained using the method based on the salicylate ISFET device and the classical ISE are in good agreement with the nominal values given by the manufacturers and with the values obtained by using the volumetric method (samples 2 and 3). However, it should be noted that the volumetric method results are quite inaccurate when other acids are present so that samples 1 and 4 were not analysed for this reason.

It can be concluded that the method employing the salicylate ISFET device, described in this paper is simpler, faster and more accurate than the classical volumetric method or spectrophotometric methods [7] since it does not require complicated separation procedures when interfering compounds or coloured components are present.

In recent years, as stated in the Introduction, several sensors for the determination of salicylate have been proposed. The linearity range of the ISFET described in this paper is similar to that one of the best performing sensors described in the literature. Enzymatic sensors, based on salicylate hydrolase and on different

Table 7
Recovery of acetylsalicylic acid in drugs and salicylic acid in ointments. Comparison of the results obtained by the salicylate ISFET and by the classical salicylate ISE

	ISFET						ISE					
Sample	Found value ($mg\ l^{-1}$)	RSD%	Standard added ($mg\ l^{-1}$)	Found total value ($mg\ l^{-1}$)	RSD%	Recovery %	Found value ($mg\ l^{-1}$)	RSD%	Standard added ($mg\ l^{-1}$)	Found total value ($mg\ l^{-1}$)	RSD%	Recovery %
Acetylsalicylic acid												
1	396	1.7	330	714	3.7	98.3	390	2.1	330	711	2.3	98.8
2	289	2.4	253	527	2.3	97.2	288	1.8	253	522	1.7	96.5
Salicylic acid												
3	227	6.3	253	484	3.1	100.6	229	6.4	253	483	2.3	100.2
4	238	2.6	253	468	1.7	95.3	240	3.1	253	488	2.5	99.0

Table 8
Analysis of acetylsalicylic acid in drugs and salicylic acid in ointments. Comparison of the results obtained by salicylate ISFET, by classical salicylate ISE and by volumetric method. Relative standard deviation values are reported in square brackets

Sample	Volumetric method (% w/w) (*a*)	Clasical ISE (% w/w) (*b*)	ISFET (% w/w) (*c*)	$\frac{b-a}{a}$ %	$\frac{c-a}{a}$ %	$\frac{c-b}{b}$ %
Acetylsalicylic acid						
1	—	12.3 [1.4]	12.4 [1.7]	—	—	+0.8
2	76.1 [2.3]	78.0 [2.0]	78.3 [2.6]	+2.5	+2.8	+0.4
Salicylic acid						
3	22.2 [6.2]	22.8 [4.4]	22.7 [7.1]	+2.7	+2.2	−0.4
4	—	18.5 [1.7]	18.3 [2.4]	—	—	−1.1

kinds of amperometric electrodes [15–17, 25], show, in general, a better specificity but a much longer response time. Liquid, or polymeric membrane ISEs [18, 26–31] are based on different electroactive species (Aliquat 336S, Nitron, different ammonium salts, etc.); the TDDAS exchanger we used here for both the classical ISE and the ISFET device seems to be among the best electroactive species proposed up to now. Finally, the ISFET shows a good response time, also with respect to the ISEs, and an excellent selectivity; it can be easily miniaturized and readily used in sensor-arrays for the simultaneous determination of different substrates.

Conclusion

A new salicylate ISFET was prepared. The sensitive membrane of the sensor consists of PVC, a proper plasticizer (DBP) and the exchanger (TDDAS). The linearity range is 5×10^{-5}–1.5×10^{-2} M and the slope of the calibration curve is about 49 ΔmV/$\Delta\log C$ for the salicylic acid while the values are 7×10^{-5}–1.5×10^{-2} M and 47 ΔmV/$\Delta\log C$, respectively, for acetylsalicylic acid. The response time is $\leq$20 s for both the substances. The sensor can operate in the pH range 6.9–12.7, with 9.0 being the optimum pH value. With the exception of the phthalate and the nitrate, other substances commonly present in commercial pharmaceutical formulations do not interfere with the determination of the compounds of interest so that the method based on the salicylate ISFET is simple, fast, accurate and highly selective for the determination of acetylsalicylic and salicylic acid in drugs.

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