FIA POTENTIOMETRIC DETERMINATION OF SALICYLATE IN PHARMACEUTICAL PREPARATIONS WITH A TUBULAR DETECTOR

José L.F.C. Lima*, M. Conceição B.M.Montenegro and A.M. Roque da Silva
Physical Chemistry Department
Faculty of Pharmacy
4000, Porto, Portugal

ABSTRACT

This paper describes the construction of a salicylate tubular poten-
tiometric detector for flow injection analysis (FIA) in which the PVC
membrane is applied directly over a conducting support consisting of a
mixture of an epoxy resin and graphite. The main working characteristics
of this device are presented and its behaviour compared with a similarly-
constructed, conventionally-shaped electrode.

Reference is made to its use in the determination of the primary ion or
the acetylsalicylic acid in pharmaceutical preparations (after hydrolysis);
the results thus obtained are compared to those provided by the British
Pharmacopaeia (B.P.) method.

(*) To whom correspondence should be addressed

INTRODUCTION

The salicylic and acetylsalicylic acid determination in pharmaceutical preparations requires considerable work in the control laboratories of the pharmaceutical industry. Official methods, namely those proposed by the British Pharmacopaeia [1], are usualy based on time-consuming and tedious titrimetric procedures which in itself justify the search for speedier and automatic methods.

Flow injection analysis (FIA) has proven to be an easily implemented automatic method that can be applied to many fields, namely to the analysis of pharmaceutical preparations [2] in which the determination of salicylic and acetylsaliciylic acid are no exception [3,4].

The use of ion-selective electrodes has also been evaluated with a view to finding simple analytical methods, as in many cases they permit the direct determination of species in pharmaceutical preparations without the need for complex sample preparations [5,6].

This paper describes the construction and assessment of a tubular potentiometric detector incorporating a reference electrode for use in FIA manifolds, thus grouping in a same process the two aforementioned advantageous procedures and, at the same time, overcoming the difficulties that are inherent to the use of conventionally-shaped selective electrodes as FIA detectors.

EXPERIMENTAL

Reagents and Standards

All the chemicals were of analytical-reagent grade and were used without any additional purification, except for tetraoctylammonium bromide which was recrystallized from ethyl acetate and later vacuum dried.

The stock solutions of the species used were prepared by weighing the respective salts and, after dilution with de-ionized water (specific conductance less than 0.1 μS cm^{-1}), used to prepare the less concentrated solutions.

Apparatus

The potentiometric measurements for assessing the response characteristics of the conventionally-shaped electrodes were carried out with a Crison 517 digital potentiometer (sensitivity ±0.1mV) together with an Orion 605 electrode switcher, both coupled to a Metrohm E 586 chart recorder to determine the electrodes response time.

For batch determinations, an Orion 902000 double-junction reference electrode was used with $0.033M$ sodium sulphate in the outer compartment. The pH measurements used for the Reilley diagram determination were carried out with a Phillips GAH 110 glass electrode.

Volume measurements of the solution were carried out with Gilson P100, P1000, and P5000 pipettes in which the volume could be regulated.

The FIA manifold included the Gilson Miniplus 2 peristaltic pump, a Rheodyne 5020 injection valve, and the connections were made by teflon tubing (0.8 mm ID). The grounding electrodes were a stainless steel tube (0.8 mm ID) which was earthed and this, as well as the joints, were home--made [7].

Although the majority of the determinations were performed by using a manual valve, we also tested the possibility of constructing a system which could operate automatically. In the latter case, we added a microcomputer-controlled Gilson 221 auto-sample and a Universal Valve Switching Module of the same brand.

The range of dispersion of the FIA system was determined through measurements carried out with a Bausch & Lomb Spectronic 21 spectrophotometer equipped with a Hellma 178.713 QS 8µl flow cell.

Preparation of the sensor and the membranes

The tetraoctylammonium salicylate was prepared by dissolving 0.19 g of tetraoctylammonium bromide in 1.9 g of o-nitrophenyloctylether in approximately 5 ml of chloroform.This solution was shaken with 25 ml of a 0.1 M sodium salicylate aqueous solution and the operation repeated 6 times in order to obtain the exchange between the ammonium salt bromide

and the salicylate.

After the last extraction process, the organic and the aqueous phases were separated and the chloroform contained therein evaporated by a nitrogen current and dried over anhydrous sodium sulphate to produce a solution of approximately 10% (w/w) tetraoctylammonium salicylate in o-nitrophenyloctylether.

The membranes for the tubular detectors and the conventionally-shaped electrodes were obtained by immobilizing the sensor in PVC. The final membrane composition was approximately 30% (w/w) of PVC and 70% (w/w) of the sensor solution.

Preparation of the all-solid-state electrode and the FIA potentiometric detector

The all-solid-state selective electrode was prepared in accordance with a technique described elsewhere [8], but substituting the silver-based conductive epoxy resin by a mixture (0.2 : 0.4 in w/w) of graphite (50μ granulometry, Merck) and a non-conductive epoxy resin (Araldite M and HR Hardener, both from Ciba-Geigy).

The potentiometric detector used for the FIA determinations (Fig.1) included a series of improvements over the nitrate-sensitive tubular electrode previous described [9], namely the inclusion of a reference electrode and the modification of the conductive support.

The 1 cm-long sensing element (A) is fixed by pressing it against the flanged ends of the FIA system tubes with two perspex plates (B and C), one of these (C) of which houses the reference electrode (D). The latter consists of a silver wire that is electrolytically coated with silver chloride and immersed in a small reservoir (E) containing a saturated solution of potassium chloride.

The sensing unit consisting of a perspex tube with a 1 cm and 0.9 cm internal and external diameter, respectively, is filled with the same conducting mixture used as a support in the construction of conventionally-shaped electrodes. After it has hardened inside the tube, its base and top are covered with a thin layer of non-conductive epoxy to prevent any
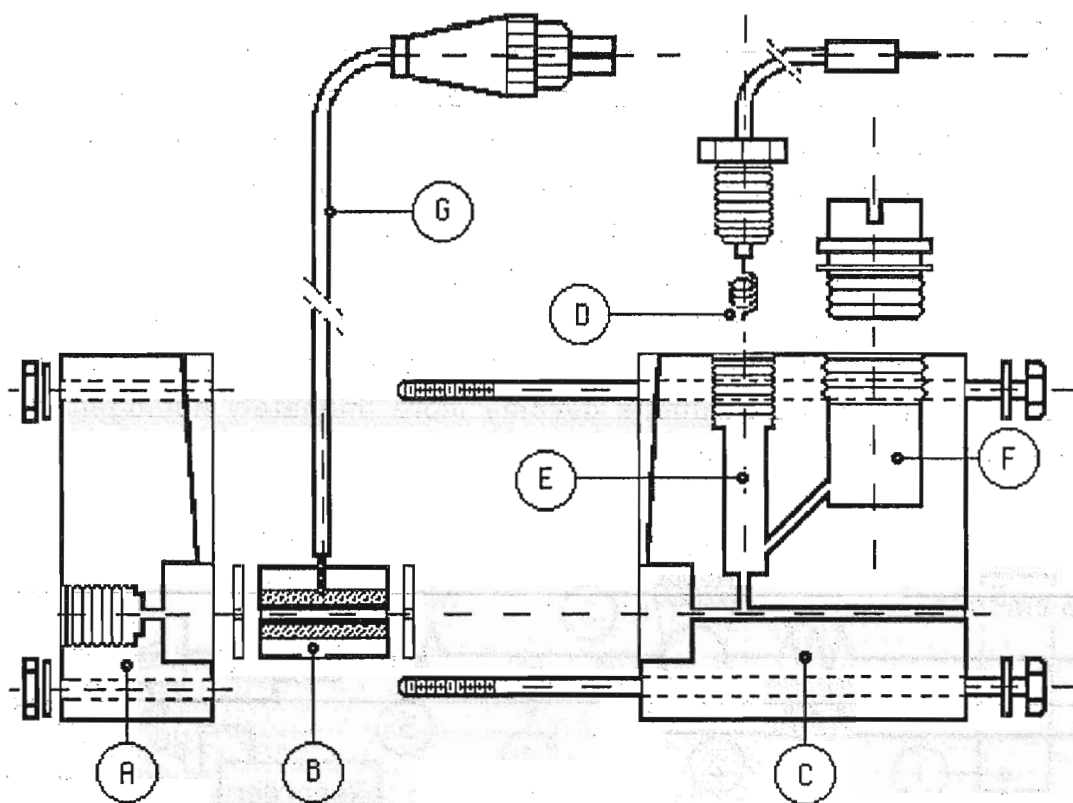
Fig.1 - Tubular detector design: (A) Perspex support piece; (B) sensing unit; (C) perspex support piece with reservoirs; (D) reference electrode; (E) reference electrode reservoir; (F) reservoir

contact between the conductor support and the solution which would lead to the occurrence of mixed potentials. Finally, the conductor support is drilled longitudinally with a 1.2 mm drill and the cavity activated, droopwise, with a solution of the PVC, THF and ion-exchanger solution as described previously [9].

Successive applications of the membrane in the cavity of the sensing unit result in a final internal diameter similar to that of the teflon tubes used in the construction of the FIA manifold.

FIA manifold

The same FIA manifold (Fig.2) was used for assessing the working characteristics of the tubular detector and for the determinations in the pharmaceutical preparations. The device includes two channels through which solutions with the same flow rate (5.6 ml/min) are introduced. A 200μl samples flows through one of these until it is meets with the solution for adjusting the conditions for measurement, which is introduced through the other channel. A 50 cm-long mixing coil is placed at this point to ensure that the two solutions become more intimately homogenized before reaching the detector.
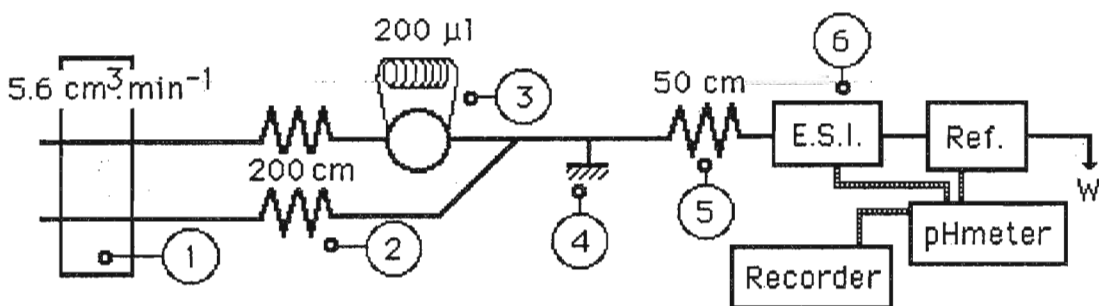

Fig. 2. Flow injection manifold: 1) Peristaltic pump; 2) Pulse dampeners; 3) Injection valve; 4) Grounding electrode; 5) mixing coil; 6) tubular detector.

A 5×10^{-5} M sodium salicylate solution is introduced through channel Q_1 to provide the baseline stabilization and to carry the sample to the point of confluence. A 0.066 M potassium sulphate solution is introduced through the channel Q_2 when assessing the working characteristics of the electrodes. A solution with 10^{-2} M of borax and 4×10^{-1} M of ammonium sulphate is introduced when determining salicylate in pharmaceutical preparations.

The dispersion value within this manifold is 2.1 when assessed according to the Ruzicka procedure [10], by substituting the potentiometric detector by spectrophotometer with a flow cell and making the measurements at a wave length corresponding to the maximun absorption of a dye solution introduced into the system for this purpose.

Sample Preparation

The tablets in which the amount of the active ingredient were determined were crushed and directly dissolved in water for salicylate determinations or subjected to hydrolisis in the case of the acetylsalicylic acid.

The solutions thus prepared and with a salicylate anion concentration of approximately 10^{-3} M, were injected with no further changes into the FIA manifold, within which we adjusted the pH and ionic strength. Direct potentiometry measurements were performed on samples to which the same volume of a 10^{-2} M borax solution of 10^{-2} M and 4×10^{-1} M solution of ammonium sulphate were added.

RESULTS AND DISCUSSION

Conventionally-shaped Electrode Behaviour

The working characteristics of the conventionally-shaped electrode without an internal reference solution are reported in Table 1, together with the values of the same parameters obtained with tubular detectors, which are as a whole, similar to those obtained with the best existing electrodes sensitive to this species [3,11-26].

The stability of the electrode response through a working day is similar to that usually obtained with mobile carrier electrodes, except for the first days after their construction during which we observed a drift of potential values that later stabilized. As already discussed elsewhere [27,28], this is due to the internal reference system of this type of electrodes, as happens with coated wire electrodes [29].

The long life of these units (approximately 12 months during which they were systematically kept immersed in a 0.1 M salicylate solution) is especially noteworthy. It is considerably greater than that of electrodes with an internal reference solution, which would confirm recent results obtained in a comparative study of barium electrodes with and without an internal reference solution [28]. This is a consequence of the fact that only

Table 1- Response characteristics of the salycilate conventionally-shaped and tubular electrode.

	conventionally-shaped	tubular electrode
Lower limit of linear response	2×10^{-4} M	1×10^{-4} M
Pratical limit of detection	5×10^{-4} M	2×10^{-5} M
Efective pH range [a]	6-12	6-9
Slope (mV/decade)	-60 ± 1	-60 ± 1
Response time (s)	<30	
Potencial stability [b] (mV/day)	± 1	± 0.2
Operational lifetime (months)	>11	>6

a) Obtained in 0.1 M salicylate solutions
b) Values obtained 3 days after construction

one membrane surface is in contact with the solutions, there thus being lesser loss of the sensor from the membrane, as opposed to what happens with internal reference solution electrodes in which the net hydrodynamic pressure must also be taken into account.

The lesser loss of sensor from the membrane of the electrodes without an internal reference solution is important when considering usage of this process as a starting procedure for the construction of tubular detectors to be incorporated in FIA manifolds.

The working characteristics of the detectors (Table 1) were assessed, using the manifold shown in Fig.2, according to the procedures previously described for a nitrate sensitive, sandwich-type detector [30].

The determination of the most convenient sample injection volume was obtained by varying the injected volume between 50 and 250 μl. The value decided upon was 200μl. In effect, changes in the injection volume between 50μl and 200μl did not affected the analytical signal more than 10%. Values of 200μl gave a signal magnitude which corresponded to a potential similar to that of the steady-state, which was determined by the injection of an extremely large volume (2000μl).

Injection values greater than those chosen, in addition to presenting no significant advantages as regards the amplitude of the signal, unnecessarily compromise the sampling rate due to the slow return of the analytical signal to the baseline.

The working characteristics of the detector when this is assessed under the aforementioned conditions, are similar or even better than those of conventionally-shaped electrodes, namely the potentiometric selectivity coefficients values (Table 2), considering that the values obtained refered to the concentration of the solutions that are introduced into the system and not to the plug concentration when it reaches the detector.

The most significant difference in the working characteristics between this detector and the conventionally-shaped electrodes is a decrease in the amplitude of the operational plateau of the Reilley diagrammes which, in the case of the tubular detectors, is approximately three pH units less extensive, as a consequence of the alkaline zone decrease. This effect is most probably due to the greater hydroxide mobility which, at the sensing surface of the tubular detector, causes a greater ratio between the concentration of the hydroxide and the salicylate than that suggested by the pH of the solution that is introduced into the manifold.

The detector responded very rapidly to variations in the salicylate concentration, thus permitting a sampling rate of approximately 120 samples/hour, taking into account the entire range of concentrations in which electrode evaluations were performed, and that the primary ion was

Table 2 - Salicylate selectivity coefficients for the conventionally-shaped and tubular electrode

Interfering species	conventionally-shaped [a]			tubular electrode [b]		
	$10^{-3}M$	$10^{-2}M$	$10^{-1}M$	$10^{-3}M$	$10^{-2}M$	$10^{-1}M$
Chloride	-0.93±0.21	-1.87±0.17	-2.74±0.13	-1.93±0.03	-2.22±0.05	-2.71±0.11
Nitrate	-0.57±0.07	-0.96±0.05	-1.36±0.04	-0.42±0.08	-0.71±0.04	-1.02±0.02
Sulphate	-2.55±0.11	-2.73±0.05	-3.26±0.09	c)	c)	c)
Acetate	-1.80±0.26	-2.71±0.23	-2.98±0.31	d)	d)	d)
Nicotinate	-1.93±0.37	-3.09±0.35	-3.49±0.31	-2.23±0.09	-2.52±0.09	-3.21±0.09

a) Average of 6 values (2 determinations with 3 electrodes)
b) Average of 4 values (2 determinations with 2 tubular electrodes)
c) Sulphate was used as carrier
d) Very low interference effect

present in the carrier at a concentration of $5x10^{-5}$ M. In those samples in which the concentration of the salicylate anion did not exceed $10^{-2}M$, the speed of the response is even greater and may lead to sampling rates of up to 200 samples/hour.

Should one wish to use the detector for measuring high concentrations of the salicylate, the sampling rate may be increased even further by increasing the concentration of the salicylate in the carrier, which obviously compromises the values of the lower limit of the linear response.

During those periods in which the tubular detectors were in current use, these were conditioned in a 0.1 M salicylate solution. When not in use for long periods, they were left dry in the open air without any further precautions. When next required, these must be conditioned with the aforementioned solution for 15 minutes which is sufficient for the detectors to regain their working characteristics.

The tubular detectors used in this study maintained their working characteristics over more than 6 months of intermittent use . As is the case with conventionally-shaped electrodes, the end of their lifetime was identified by a loss of their working characteristics, namely a decrease in the slope, in response time, and in potential reproducibility. When there are signs of a deficiency, the design of these detectors makes it easy to substitute the sensing module (Fig.1), with little loss of working time.

The sensing modules are easily recovered by mechanically removing the PVC membrane, sanding the conductive support until it is clean, and applying a new membrane by the method described herein.

Determination of Salicylate and Acetylsalicylate in Tablets

The quality of the salicylic and acetylsalicylic determinations in pharmaceutical preparations was assessed by comparing the results obtained with the FIA manifold with the tubular detector, to those obtained by direct potentiometry performed with the electrodes without internal reference solution and those given by the conventional procedures described in the British Pharmacopaeia [1].

The FIA determinations were made with the aforementioned manifold (Fig.2) in which water was introduced through channel Q_1 and at a similar rate, the same solution used to adjust the ionic strength and the pH in the determinations performed by direct potentiometry, through channel Q_2.

The results of the FIA and the direct potentiometric determinations of acetylsalicylate are in good agreement with each other and with those obtained with the B.P. method (Table 3).

In the case of those pharmaceutical preparations that contain salicylate as an active ingredient and for which the B.P. does not expressly

Table 3 - Mean values obtained by direct potentiometry, FIA and British Pharmacopaeia (B. P.) methods for the assay of acetyl-salicylic acid in some tablets.

| Brand | Salicylate (%) [a] | | |
	Potentiometry	FIA	B.P.method
Aspirine Bayer	85.3 ± 0.8	84.8 ± 0.6	84.0 ± 1.0
Toldex Retard	93.1± 2.0	92.4 ± 2.0	93.7± 2.0
Salicilyna	83.6 ± 1.0	83.7 ± 1.0	83.7± 0.6
AAS	92.6 ± 2.0	91.8 ± 1.0	91.2 ±2.0
Toldex	70.7 ± 0.9	72.0 ±1.0	72.8 ± 1.6

a) Mean and standard deviation for three determination with 3 different samples of the same tablet.

indicate an analytical procedure, the quality of the results was assessed by determining the recovery ratio which was always found within a 100±2% interval.

CONCLUSIONS

The new design for a simple and inexpensive tubular potentiometric detector for FIA incorporating a reference electrode presents clear advantages over the use of conventionally-shaped electrodes in a cascade arrangement, namely because this is more easily assembled and maintained. Moreover, the central sensing unit itself is easily and rapidly

substituted when there are signs of working deficiencies.

The results obtained show that under the experimental conditions described herein, the tubular detectors presented working characteristics similar to those of conventionally-shaped electrodes with a similar construction and sensor. Of special interest are the potential reproducibility and the long lifetime of the tubular electrodes.

The conventionally-shaped electrode described herein presents working characteristics similar or even better than those of other salicylate anion-sensitive electrodes [3,11-26].

Moreover, this type of construction offers additional advantages such as a greater economy of the sensor, long lifetimes which are greater than 11 months, a more robust assembly, and easier maintenance.

Finally, the applicability of these detectors in FIA manifolds that can, be easily used in the determination of salicylate and acetylsalicylic acid in pharmaceutical preparations is worth highlighting as they yield results that are similar to those obtained by direct potentiometry or by the official method [1].

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