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Potentiometric determination of acetylsalicylic acid by sequential injection analysis (SIA) using a tubular salicylate-selective electrode

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Abstract

This paper deals with the development of an automated procedure for formulation assays and dissolution tests based on a sequential injection analysis (SIA) system involving an ion-selective electrode as sensing device. Construction of a tubular salicylate (Sal) selective electrode suitable for potentiometric determination of acetylsalicylic acid (Asa) in pharmaceutical formulations is described. The flow-through electrode is formed by a PVC membrane containing 29.2% (w/w) PVC, 5.8% (w/w) tetraoctylammonium salicylate (ionic sensor), 58.5% *o*-nitrophenyloctylether (plasticizer) and 6.5% (w/w) *p*-tert-octylphenol (stabilising additive which increases electrode selectivity). The calibration range is 0.05–10 mM Sal, the limit of detection (LOD) is 0.05 mM Sal, the slope is 56.0 mV per decade at 22°C. The R.S.D. is 0.20% (15 readings) when determining 2.5 mM Sal in standard solution. The electrode is used for sensing Asa after its on-line chemical hydrolysis to Sal in a SIA system. The sampling rate is 6 h^{-1} but for the dissolution tests the frequency is increased to 20 h^{-1}. The SIA set-up is employed for the assay of Asa in plain tablets, composed tablets and effervescent tablets and for performing dissolution tests of normal and sustained release tablets. Results obtained by this technique compare well with those required by the US Pharmacopoeia XXIV.
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Keywords: SIA; Potentiometric detection; Salicylate-selective tubular electrode; Acetylsalicylic acid; Dissolution tests; Pharmaceutical formulations

1. Introduction

Despite the fact that acetylsalicylic acid (Asa) is one of the oldest chemical drugs employed as the active principle in numerous pharmaceutical

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preparations, its rapid and reliable assay in real pharmaceuticals is often far from straightforward. Because of its unstable ester functionality the Asa is easily hydrolysed to salicylate (Sal) in solutions and even the bulk substance undergoes gradual decomposition upon prolonged storage.

Therefore, analytical methods enabling simultaneous quantitation of Asa as the active principle and minor amounts of Sal as the impurity are of great value in the field of quality control of drugs. It is obvious that for such a purpose separation techniques, e.g. HPLC with spectrophotometric detection, are most suitable though often time consuming (see Refs. [1–6]). Gas chromatography was utilised for the assay of Asa and Sal in tablets [7] and serum matrix [8].

Non-separation methods for the determination of Asa often involve conversion of Asa to Sal and subsequent instrumental assay of the Sal produced. Spectrophotometry was proposed for the determination of Asa or Sal after Trinder or another colour reaction [9–12]. Resolution between Asa and other active substances contained in the same formulations, such as paracetamol and caffeine, can be accomplished by diode-array spectrophotometry [13,14].

Spectrophotometry is also useful for performing dissolution studies of pharmaceutical formulations containing salicylate [12,14]. Derivative fluorimetry was proposed for the determination of Sal and salicyluric acid as metabolites of Asa occurring in body fluids [15]. Enzymic conversion of Sal to catechol using salicylate hydroxylase and tyrosinase was employed for spectrophotometric [16] or amperometric [17] assays of Sal or Asa in biological samples. Potentiometry with salicylate-selective electrodes based on ion-selective liquid, pseudo-liquid or polymeric membranes [18–24] proved to be a convenient method for the quantitation of Sal in pharmaceuticals [19–26]. Some of Asa and Sal analyses were carried out by automated non-separation flow methods such as flow injection analysis (FIA) [12,13,17,20,23] or sequential injection analysis (SIA) [14] that are convenient tools for carrying out dissolution studies of active principles in pharmaceutical formulations (measurement of dissolution profiles).

We have shown previously that a salicylate-selective electrode can be successfully employed for potentiometric FIA assay of Asa in pharmaceuticals after its conversion to Sal by off-line hydrolysis [20]. Our present paper deals with the construction of a novel tubular salicylate-selective electrode with improved sensor properties. Such an electrode is utilised for fully automated potentiometric SIA determination of Asa in pharmaceutical formulations involving on-line hydrolysis of Asa directly in the SIA system. Our results are compared with those obtained by the official HPLC method required by the US Pharmacopoeia XXIV [27] or by spectrophotometry [28]. The convenience of our method is exemplified by successful automated potentiometric SIA dissolution tests of Asa in multi-component pharmaceutical formulations where the conventional non-separation UV spectrophotometric detection may be prone to failure due to possible interferences from the accompanying active principles.

2. Experimental

2.1. Chemicals and reagents

All chemicals for the electrode construction, optimisation procedures and final determination of Asa were of analytical grade and they were used without further purification. Tetraoctylammonium bromide (Fluka), *o*-nitrophenyloctylether (Fluka), *p*-*tert*-octylphenol (Fluka), poly(vinyl-chloride) of high molecular weight (Fluka), tetrahydrofuran (Riedel-deHaen), Asa (Sigma) and Sal (Sigma) were used. De-ionised water purified by a Millipore (Milli-Q) apparatus was utilised throughout.

Standard solutions of Sal and Asa were prepared from weighed amounts of sodium salicylate and acetylsalicylic acid, respectively, if not stated otherwise. Fresh Asa solutions were always prepared to avoid the hydrolysis of Asa in stock solutions. The ionic strength adjuster was a sodium sulphate solution (0.033 M) and the pH and ionic strength adjuster was a phosphate buffer (pH = 8; $I = 0.1$ M). These solutions were selected according to both the selectivity potentiometric coefficients and to pH operational range, further mentioned.

2.2. Apparatus

The SIA system employed consisted of an 8-port Vici-Valco selection valve (Cheminert C15-3118 E), a 4-channel Gilson Minipuls 3 peristaltic pump, NResearch solenoid valve (model 161 TO 31) and a Crison micro pH 2002 potentiometric detector linked to a Kipp-Zonen chart recorder. Batch pH measurements were made by another Crison pH 2002 detector equipped with a Philips GAH 110 glass electrode. For reference dissolution profile measurements a UV–vis spectrophotometric detector (PU 8625) with a Helma 100 μl flow-through cell (10 mm light path) was connected to the system. The SIA manifold involved PTFE connection tubing (0.8 mm ID).

The indicator tubular salicylate-selective membrane electrode was constructed as described elsewhere [20] and its signal was recorded against an Orion reference electrode (AgCl/Ag). The grounding electrode was fabricated from stainless steel tube of 0.8 mm ID. The SIA manifold is depicted in Fig. 1 and the time sequence of the SIA protocol for dissolution tests is presented in detail in Table 1. The SIA system was controlled by a PC running with software written in Quick-Basic.

Reference analyses were carried out on a HPLC system Varian 9012 equipped with an Alltech-Spherisorb ODS-1 column (250 × 4.6 mm) and Varian 9050 UV detector ($\lambda = 280$ nm) controlled by Star Chromatography Workstation software Varian 4.51. Dissolution tests were performed by a single-unit dissolution apparatus Erweka DT (Germany) involving a paddle agitator for stirring the dissolution medium.

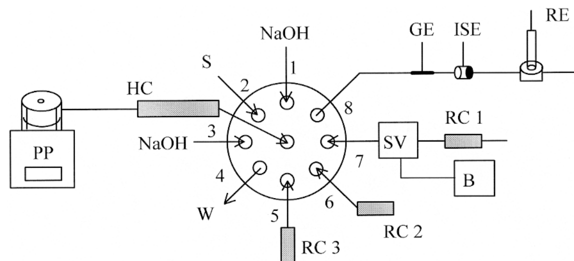

Fig. 1. Sequential injection system with peristaltic pump (PP) and selection valve; S, sample or standard; HC, holding coil 2.5 m long; W, waste; RC, reaction coils 2.0 m long; SV, solenoid valve; B, reservoir of phosphate buffer ($I = 0.9$, pH = 8); GE, grounding electrode; ISE, ion selective electrode; RE, reference electrode.

The kinetic profile of Asa hydrolysis to Sal under batch conditions was measured by a diode array spectrophotometer (HP 8453) operated with Chemstation software ($\lambda = 295$ nm).

2.3. Construction of a salicylate-selective electrode

The ionic sensor (tetraoctylammonium salicylate) was prepared by dissolving 0.19 g of tetraoctylammonium bromide in 1.9 g of *o*-nitrophenyloctylether with approximately 5 ml of chloroform. Thereafter this solution was shaken with 25 ml of aqueous 10 mM sodium salicylate and the extraction procedure was repeated six times to substitute bromide by salicylate in the liquid ion-exchanger.

Another ionic sensor was prepared by adding 0.19 g of *p*-*tert*-octylphenol to the organic phase before extraction. The presence of this compound improves the performance of carboxylate-selective electrodes since it is believed to increase the affinity of the carboxylate to the selective membrane by the establishment of hydrogen bonds between the carboxylate and OH-group of the phenol additive.

The organic phase was separated, chloroform was evaporated in a stream of nitrogen and the remaining solution was dried over anhydrous sodium sulphate to give approximately 10% (w/w) of tetraoctylammonium salicylate and 10% (w/w) of *p*-*tert*-octylphenol in *o*-nitrophenyloctylether as the sensor solution. The membrane for the tubular detector was constructed by immobilising 0.4 ml of the sensor solution in 0.18 g of PVC previously dissolved in tetrahydrofuran.

The overall composition (w/w) of the membrane with or without the additive was about 29.2 or 31.0% of PVC, 5.8 or 6.3% of tetraoctylammonium salicylate and 58.5 or 62.7% of *o*-nitrophenyloctylether and 6.5% of *p*-*tert*-octylphenol. The selective membranes were applied dropwise over conventional and tubular shaped conductive supports [20]. Before the first measurement and also when not in permanent use the salicylate-se-

Table 1
Time sequence of Asa dissolution tests by SIA-potentiometry (the 1st sample determination cycle)

Time (min:s)	SV port activated	Flow rate (ml min^{-1})	Flow direction[a]	Action
00:00	2	6	a	Tube washing
00:03	3	6	d	HC washing
00:07	1	6	a	NaOH aspiration
00:08	2	6	a	Blank sample (buffer) aspiration
00:10	4	6	a	NaOH aspiration
00:12	7	6	d	Blank sample to the RC1
00:21	2	6	d	Filter washing
00:24	3	6	d	HC washing
00:31	7	0	d	Stop-flow period started
02:49	2	6	a	Tube washing
02:51	3	6	d	HC washing
02:55	1	6	a	NaOH aspiration
02:56	2	6	a	1st Asa sample aspiration
02:58	4	6	a	NaOH aspiration
02:59	5	6	d	1st Asa sample to the RC3
03:07	2	6	d	Filter washing
03:10	3	6	d	HC washing
03:18	7	0.5	a	Blank sample pH adjustment
05:22	8	6	d	Blank sample to the detector
05:47	2	6	a	Tube washing
05:50	3	6	d	HC washing
05:57	1	6	a	NaOH aspiration
05:58	2	6	a	2nd Asa sample aspiration
06:00	4	6	a	NaOH aspiration
06:02	6	6	d	2nd Asa sample to the RC2
06:11	2	6	d	Filter washing
06:14	3	6	d	HC washing
06:21	5	6	a	1st Asa sample to the HC
06:28	7	6	d	1st Asa sample to the RC1
06:34	7	0.5	a	1st Asa sample pH adjust.
08:35	8	6	d	1st Asa sample detection

d > 1st Asa sample detection
[a] a, Aspirate; d, dispense; RC1–3, reaction coils 1–3; HC, holding coil.

lective electrode was stored in 1 mM sodium salicylate solution. Under these conditions its lifetime was more than 6 months.

2.4. Asa formulations

The amount of Asa as active principle was assayed in Aspirina tablets (500 mg of Asa per tablet, Bayer, Portugal), in Anadin Extra composed tablets with paracetamol and caffeine (300 mg of Asa, Whitehall, Portugal), in Dolviran composed tablets with caffeine and codeine (400 mg of Asa, Bayer, Portugal) and in Alka-Seltzer effervescent tablets (324 mg of Asa, Bayer, Portugal). Ten tablets of each formulation were weighed, disintegrated and an amount of the homogenised mixture corresponding to approximately 15 mg of Asa was weighed, suspended in about 100 ml of water, set aside for 30 min, filtered and diluted to the exact volume in a volumetric flask. This solution was immediately used for Asa determination.

Dissolution profiles were measured for conventional Aspirina tablets (500 mg of Asa, Bayer, Portugal) Anadin Extra composed tablets (300 mg of Asa, Whitehall, Portugal), Dolviran composed tablets (400 mg of Asa, Bayer, Portugal) and Toldex Retard sustained release tablets (650 mg

of Asa-microcapsulated, Bial, Portugal). The SIA sampling rate was increased for the Aspirina, Anadin and Dolviran tablets dissolutions to obtain readings every 3 min during the measuring period of 30 min. Sustained release tablets were measured over 9 min intervals during a period of 90 min. The dissolution medium for both tablet types was 500 ml of 0.05 M acetate buffer (pH = 4.5), agitation speed 50 rpm and temperature 37°C.

2.5. SIA system and procedures

The evaluation of the Sal-selective electrode behaviour was performed by aspirating standards from the first port of the selection valve to the holding coil. Then the direction of the carrier stream was reversed and a sample zone was pushed through the detector. The potentiometric detector comprised the grounding electrode, salicylate-selective electrode and reference electrode (see Fig. 1). Each sample was analysed in triplicate.

Among parameters assessed for the Sal-selective electrode evaluation pH, flow rate and volume of standard solutions were considered. In the optimisation experiments sodium sulphate solution was used as carrier since sulphate exhibited negligible interference towards the Sal electrode.

Asa hydrolysis proceeded after transferring the zones of reagent and sample from the holding coil to the reaction coil where the flow was stopped. After a stop-flow period sufficient for the hydrolysis of Asa the sample zone was returned to the holding coil at a low flow rate and during this step a solenoid valve was activated to mix the alkaline zone with highly concentrated phosphate buffer ($pH = 8$, $I = 0.9$) to adjust for appropriate pH. Then the flow was reversed and the sample was propelled through the detector.

Asa was initially converted to Sal by alkaline hydrolysis with 0.2 M sodium hydroxide. The yield of Sal was optimised with respect to the volume of sodium hydroxide, length and type of reaction coils, stop flow period and flow rates. The hydrolysis of Asa to Sal was followed by spectrophotometry during the optimisation procedure. The respective amount of Asa converted to Sal was compared by kinetic measurement of hydrolysis process with spectrophotometric detection under flow and batch conditions at $\lambda = 295$ nm.

Determination of Asa in pharmaceuticals was performed after adjusting the concentrations of analyte in the test solutions to fall within the middle of the calibration curve. Each formulation was always analysed twice with new calibration and triplicate injection of the test and standard solutions.

For single-component formulations the results obtained by potentiometry were compared by using spectrophotometric detection ($\lambda = 265$ nm) in the same SIA system and for all types of tablets reference assays were performed by an official HPLC method [27]. Samples and standards were dissolved in methanol–acetic acid (95:5 v/v), the mobile phase was water–methanol–acetic acid (69:28:3 v/v/v) and flow rate 2 ml min^{-1}. These conditions complied with the US Pharmacopoeia XXIV for Asa-containing composed tablets with paracetamol and caffeine, just the analytical wavelength was changed to 280 nm in accordance with the article on Asa-containing tablets [28].

Dissolution tests were carried out with a single tablet for each formulation packing and the Asa standards were dissolved in the same buffer that was used as a dissolution medium. Two dissolution measurements were performed for each type of Asa formulation, the reference dissolution test was also carried out in duplicate by using spectrophotometric detection [28].

3. Results and discussion

3.1. Characteristics of the salicylate detector

Optimum value of the Sal plug volume and of the flow rate were 350 μl and 6 ml min^{-1}, respectively. These values ensured minimum dispersion in the flow system and highly reproducible potential readings. Final calibrations for Sal were carried out in phosphate buffer ($pH = 8$, $I = 0.1$) with a background concentration of 0.1 μM Sal ensuring stable baseline of the electrode signal. Nernstian calibration range was rectilinear for

Table 2
Response characteristics of the conventionally shaped and tubular salicylate electrodes with and without the additive in the membrane

	Conventional	Conventional + additive	Tubular [20]	Tubular + additive
LOQ (M)	2.8×10^{-4}	1.1×10^{-4}	1×10^{-4}	5×10^{-5}
LOD (M)	1.2×10^{-4}	7.8×10^{-5}	2×10^{-5}	5×10^{-5}
Effective pH range[a]	5–12	6–11	6–9	6–9
Slope (mV per decade)	-58.7 ± 1.4	-58.4 ± 0.7	-60.0 ± 1.0	-56.0 ± 0.6
Response time (s)	<5	<5	<5	<5
Reproducibility (mV)	±0.4	±0.3	–	±0.3
R^2	>0.99908	>0.99930	–	>0.99990

[a] Measured only with ionic strength adjustment.

0.05–10 mM Sal in standard solutions ($R^2=0.9999$). The limit of detection (LOD) was 0.05 mM Sal, the slope was 56.0 mV per decade and the R.S.D. was 0.20% (15 readings) when determining 2.5 mM Sal in standard solution.

Response characteristics of the conventionally shaped and tubular salicylate electrodes with and without the additive in the sensor membrane are cited in Table 2. General working and calibration parameters are shown to compare the characteristic features of the salicylate electrodes. The limit of detection decreased upon the application of the additive; its stabilising effect was also observed. The tubular electrode exhibited lower values of linear response and detection limit compared to a conventionally shaped electrode, thus enabling us to measure lower Sal concentrations.

Effective pH range was significantly wider for the conventional Sal-selective electrode without the additive. This effect is probably caused by higher OH^- ion mobility at the sensing surface of the tubular electrode resulting in a higher hydroxide/salicylate concentration ratio which exceeds that suggested by the pH of the solution that was introduced into the manifold. Nevertheless, the tubular electrode with the additive could be used in the pH range from 6 to 9 (see Fig. 2) which was large enough for practical applications.

Other parameters such as the slope, response time, reproducibility and correlation coefficient were similar for all four types of Sal electrodes. The calibration curve slope values increased when going from the conventional to tubular electrodes but the application of the additive in the tubular electrode lowered the value of this parameter. All electrodes responded rapidly to variations in the Sal concentrations with sufficient reproducibility.

As for potential interferences from other ions bearing the same charge as Sal we compared the behaviour of the tubular electrode with the additive in the sensing membrane with conventional and tubular electrodes without the additives which were used in a previous study [20]. The data obtained by these experiments served for selecting an appropriate buffer system in the carrier stream.

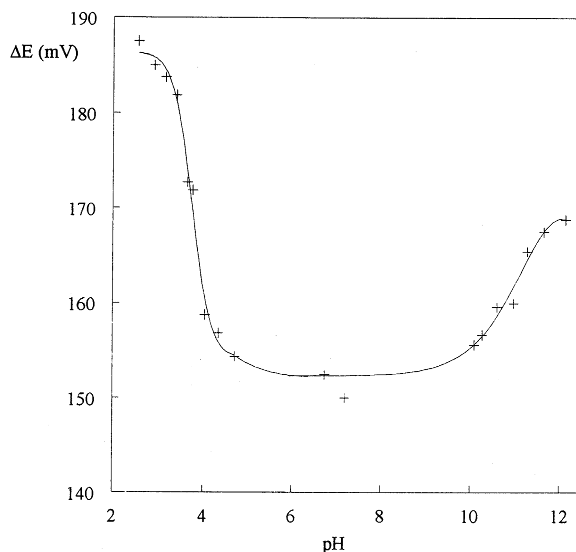

Fig. 2. Effect of pH on the potential response of tubular salicylate-selective electrode (with *p-tert*-octylphenol additive); c(Sal) = 0.01 M.

Table 3
Potentiometric selectivity coefficients for tubular salicylate electrode; potential interferents examined: acetate, acetylsalicylate, chloride and nitrate

Interferents	Log $K^{pot}_{A,B}$		
	10^{-3} M Sal	5×10^{-3} M Sal	10^{-2} M Sal
Acetate	-2.027 ± 0.004	-2.661 ± 0.004	-2.902 ± 0.013
Chloride	-1.810 ± 0.002	-2.095 ± 0.007	-2.204 ± 0.006
Nitrate	-0.701 ± 0.005	-0.928 ± 0.023	-1.019 ± 0.010
	10^{-4} M Sal	5×10^{-4} M Sal	10^{-3} M Sal
Acetylsalicylate	-0.654 ± 0.019	-1.094 ± 0.016	-1.268 ± 0.000

Here the interferents examined were acetate, chloride, nitrate and acetylsalicylate. The calculated values of the selectivity coefficients [29] are summarised in Table 3. Acetate exhibited lower interference towards the additive-containing tubular electrode compared to the conventional Sal electrode. The interfering effect of chloride decreased in the order: conventional electrode — additive-containing tubular electrode — tubular electrode without the additive. Nitrate exhibited the lowest interference effect for the tubular electrode with the additive.

The selectivity coefficient value of acetylsalicylate seemed to give us the chance to use the matched-potential method [30] for simultaneous speciation of Asa and Sal. Unfortunately the potentiometric interference ratio which, in contrast to the selectivity coefficient, is concentration dependent, was found to be too small, see Table 4. Consequently, the signals of Asa and Sal could not be resolved by multivariate calibrations and, therefore, we decided to use the salicylate-selective electrode for determining Asa after its hydrolysis to Sal.

Table 4
Potentiometric interference ratio of acetylsalicylate

Acetylsalicylate	Log $K^{pot}_{A,B}$	
	5×10^{-5} M Sal	10^{-4} M Sal
5×10^{-5}	0.436	0.468
10^{-4}	0.275	0.322
5×10^{-4}	0.074	0.042
10^{-3}	0.040	0.019

3.2. Optimisation of Asa conversion to Sal

Here the parameters optimised were concentration of sodium hydroxide as the reagent (0.05–0.2 M), reagent volume and its aspiration pattern, sample volume, reaction coil length (60–200 cm) and its geometry (straight or coiled) and flow rate or duration of the stop-flow period in the hydrolysis step. To ensure maximum yield of Sal a 200-μl plug of the sample solution was sandwiched between two zones of 0.2 M NaOH, their volumes being 100 and 80 μl; these three zones were passed to a 2-m reaction coil (coiled geometry, but this was not a critical prerequisite). After a stop-flow period of 3–4 min about 80% of Asa was converted to Sal (see Fig. 3); as follows from the selectivity data, the unreacted Asa should not interfere with the potentiometric detection of the produced Sal. The inset in Fig. 3 shows kinetic measurement of batch Asa hydrolysis to Sal monitored by UV spectrophotometry at 295 nm; it is evident that this kinetic curve compares well with that obtained by SIA-spectrophotometry. The residence time which is indicated in Fig. 3 means the period for which the sample plug is stopped in the reaction coil, for real reaction time about 1 min must be added (to consider aspiration and transport of the NaOH–Asa–NaOH zone to the reaction coil).

Since the hydrolysed sample contains 0.2 M NaOH, its pH has to be adjusted to optimum pH 8 before the detection of Sal; this could not be accomplished by merely mixing the strongly alkaline plug with the carrier buffer during the Sal plug transport to the detector (the carrier buffer has insufficient buffering capacity and also its proper mixing with the sample plug is impossible even at its very low flow rate). This problem has been overcome by placing a three-port solenoid valve SV between the reaction coil RC1 and the

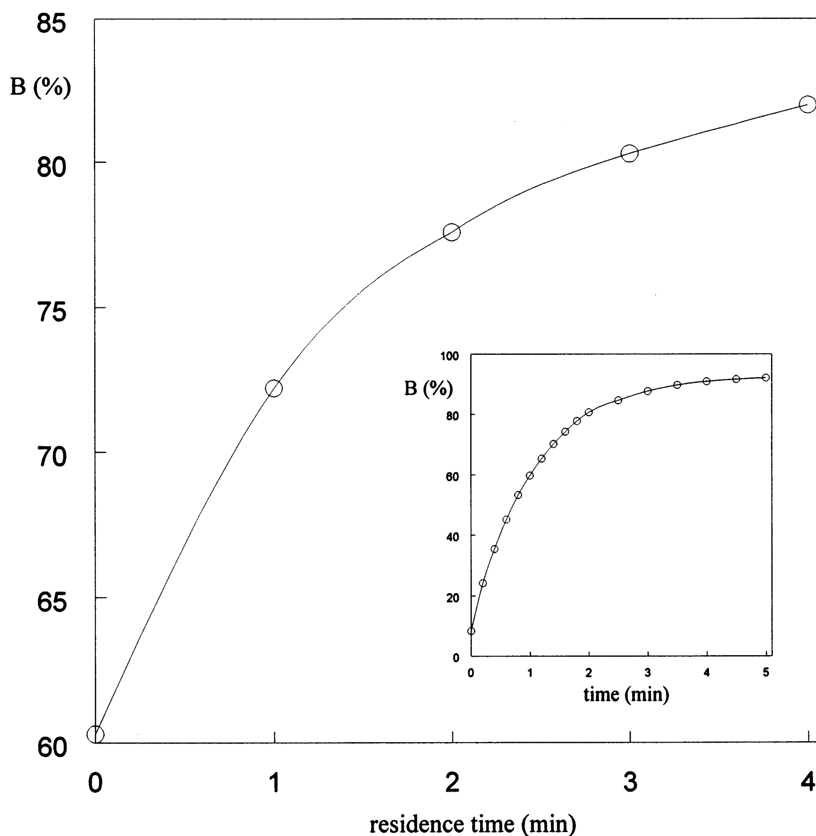

Fig. 3. Kinetics of Asa hydrolysis to Sal under flow conditions by spectrophotometry at 295 nm, c(Asa) = 1 mM, c(NaOH) = 0.2 M (residence time of the Asa–NaOH plug in the RC); inset figure: Asa hydrolysis under batch conditions, c(Asa) = 0.5 mM, c(NaOH) = 0.1 M; B, amount of Asa converted to Sal

selection valve (see Fig. 1), one inlet port being connected to the RC1 and the second one to the reservoir B containing a concentrated ($I = 0.9$) phosphate buffer solution of pH 8. During the aspiration of the hydrolysed sample plug from RC1 to the holding coil (for 2 min at a flow rate of 0.5 ml min^{-1}) the solenoid valve is operated in such a way that the two ports are activated alternately, each for 0.5 s, thus ensuring proper mixing of these two streams and the requisite pH adjustment of the Sal plug at the outlet port of the solenoid valve.

A single measuring cycle took about 8 min including the stop-flow period and final pH adjustment.

3.3. Determination of Asa in pharmaceuticals (tablets)

Calibration curves involved three points covering the concentration range of 0.5–1.0 mM of Asa. The results obtained by SIA-potentiometry, spectrophotometry and by a reference HPLC method [27] are presented in Table 5. It can be seen that the content of Asa in the formulations conforms to the requirements of USP XXIV. Student's t-test confirms that the differences between SIA-potentiometry and HPLC are statistically insignificant in all instances (t-test results do not exceed the critical value, see Table 5) while the results obtained by SIA-spectrophotometry differ

Table 5
Determination of Asa in pharmaceutical formulations[a]

Formulation	Label amount (mg per tablet)	Potentiometry/t-test[b] (mg per tablet ± R.S.D.)	Spectrophotometry/t-test[c] (mg per tablet ± R.S.D.)	HPLC (mg per tablet ± R.S.D.)
Anadin extra	300.0	307.0 ± 1.7/1.41	–	300.4 ± 1.4
Aspirina	500.0	517.2 ± 1.4/0.67	510.1 ± 1.6/1.07	513.1 ± 0.9
Dolviran	400.0	403.8 ± 0.6/1.27	–	411.7 ± 2.0
Alka-Seltzer	324.0	326.5 ± 1.8/1.57	306.6 ± 1.6/6.06	334.3 ± 1.2

[a] $t_{crit} = 2.77$ ($\nu = 4$, $\alpha = 0.05$) [31].
[b] Mean value of SIA-potentiometry ± R.S.D.(%)/t-test value for comparison with HPLC method.
[c] Mean value of SIA-spectrophotometry ± R.S.D.(%)/t-test value for comparison with the HPLC method.

significantly from these of HPLC in the case of effervescent Alka-Seltzer tablets. The SIA-spectrophotometry could not be used for the assay of Asa in the composed Anadin Extra and Dolviran tablets because the accompanying active principles (paracetamol, caffeine and codeine) interfere with the UV detection of Asa.

3.4. Dissolution tests

Dissolution measurements of conventional tablets lasted 30 min and so the sampling rate had to be increased to obtain a sufficient number of experimental points for the construction of the dissolution profiles. Two spare ports of the selection valve accommodated auxiliary reaction coils RC2 and RC3 where each sample was hydrolysed for 2 min. Meanwhile another sample was processed in RC1 and SV, in fact its pH adjustment was carried out. The 2 min stop-flow period (total reaction time about 3 min) was long enough to get 10 points for each dissolution curve (for the exact timing see Table 1). The final sample throughput was increased to 20 h^{-1}.

For sustained release tablets the sampling rate was 9 min and the whole experiment took 90 min. During the dissolution procedure additional steps were included such as purging of the sampling tube to ensure aspiration of a new portion of the dissolution liquid and cleaning of the inlet filter (this step also served to restore the dissolution liquid volume). Before each dissolution test a new calibration with four standard solutions was performed.

The dissolution profiles of selected formulations measured by SIA-potentiometry with the salicylate-selective electrode are shown in Fig. 4 together with the profiles obtained by spectrophotometry at 265 nm following an official article for Asa-containing tablets [28]. The dissolution profiles obtained by SIA-potentiometry compare well with those of the reference method even though in each experiment a different tablet was analysed.

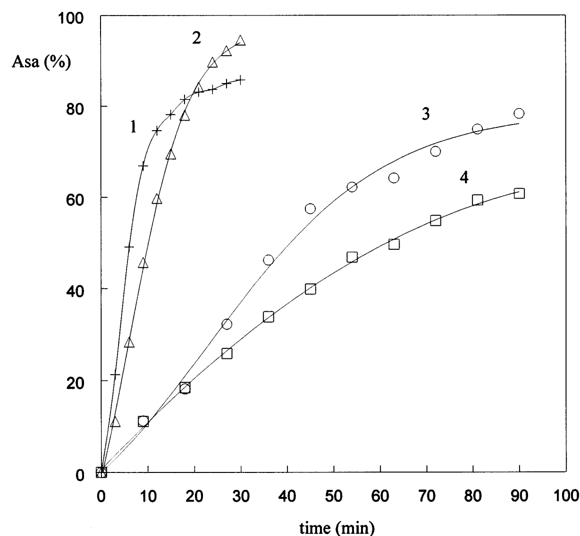

Fig. 4. Dissolution profiles for Aspirina and Toldex tablets; curve 1, Aspirina dissolution with spectrophotometric detection; curve 2, Aspirina potentiometric dissolution; curve 3, Toldex potentiometric dissolution; curve 4, Toldex spectrophotometric dissolution.

4. Conclusions

An automated sequential injection technique with potentiometric detection using a tubular salicylate-selective electrode proved to be useful for determining acetylsalicylic acid after its on-line hydrolysis to salicylate. The method could be utilised for SIA assay of Asa content in pharmaceutical preparations (including multi-component and effervescent tablets) and for automated measurement of dissolution profiles of conventional, composed and sustained release tablets containing Asa as the active principle. The results obtained by the SIA-potentiometry method compared well with established pharmacopoeial methods. Thanks to the selectivity of the detection of Asa the proposed SIA method may solve the problem of Asa-release studies of multi-component tablets where conventional UV detection often fails because of the presence of accompanying active substances as possible interferents and because of undisolved particles which have to be carefully filtered.

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