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Determination of Salicylic Acid in Pharmaceutical Formulations and Foods by Differential-pulse Voltammetry Using a Glassy Carbon Electrode

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A simple and rapid voltammetric method for the determination of salicylic acid in pharmaceutical preparations and foods has been developed. The sample was extracted using either diethyl ether or ethanol - diethyl ether and then back-extracted into 0.015 M disodium hydrogen phosphate solution. The peak current was measured using a glassy carbon electrode at 0.85 V. The working range was 0–25 p.p.m. The average recovery for ointment was 99% with a standard deviation of 5.0%. Results are reported for eight different pharmaceutical formulations.

Keywords: *Salicylic acid determination; differential-pulse voltammetry; pharmaceutical; food*

Salicylic acid is a compound used as an antimicrobial agent in many pharmaceutical preparations and foods. The pharmaceutical preparations include ointments, dusting powder and lotion. The techniques described for the determination of salicylic acid include colorimetry,[1–4] titrimetry,[5–7] UV spectrophotometry,[8,9] spectrofluorimetry,[10] gas chromatography,[11,12] direct potentiometry[13] and high-performance liquid chromatography (HPLC).[14–17] Of these, the titration methods are non-selective and subject to interference by reducing agents. The colorimetric methods, which involve the use of iron(III) to complex with salicylic acid, do not have sufficient sensitivity to determine salicylic acid down to p.p.m. levels. The HPLC methods are simple and suitable for routine analysis where many samples must be analysed.

Few voltammetric methods have been proposed for the determination of salicylic acid; Woodson[18] reported that it could be reduced in acetonitrile medium and detected down to 10 p.p.m. The purpose of this work was to develop a voltammetric method for the determination of salicylic acid in drugs and foods. The sample, such as an ointment, is first extracted by an organic solvent and then back-extracted by an alkaline medium before being analysed by direct electrochemical oxidation using a glassy carbon electrode. The results show that the method is selective, simple and salicyclic acid can be determined down to p.p.m. levels with satisfactory precision.

Experimental

Apparatus

Voltammograms were recorded with a PAR Model 174A polarographic analyser equipped with a Houston *x* - *y* recorder (RE0089). A laboratory-made working electrode made from 3 mm diameter polished glassy carbon (Atomergic Chemical), a saturated calomel reference electrode (SCE), separated from the electrolyte by a saturated potassium chloride solution, with acid resistant Vycor ends, and a platinum wire counter electrode were used. The modulation amplitude, scan rate and current range were 50 mV, 5 mV s^{-1} and 20–50 μA, respectively. The scan direction was positive and with an initial potential of +0.4 V.

Reagents

The reagents used were of analytical-reagent grade.

Standard salicylic acid solution, 300 μg ml^{-1}. Prepared by dissolving 0.0300 g of salicylic acid in 95% ethanol and diluting to 100 ml in a calibrated flask with ethanol.

Supporting electrolyte (disodium hydrogen phosphate) solution, 0.015 M. $Na_2HPO_4.12H_2O$ (5.4 g) was dissolved and diluted to 1 l with distilled water.

Hydrochloric acid solution. Prepared by mixing concentrated hydrochloric acid and distilled water (1 + 2 *V/V*).

Procedure

Preparation of sample solutions

An amount of the drug sample equivalent to 2–4 mg of salicylic acid was weighed accurately in a 250-ml beaker. Ethanol - diethyl ether (1 + 1; 100 ml) was added. Using an ultrasonic shaker, the salicylic acid was extracted from the sample. After extraction, the suspension was transferred completely into a 250-ml calibrated flask and diluted to the mark with 1 + 1 ethanol - diethyl ether. As most of the undissolved solids had settled, 25 ml of the mixture were pipetted into a 125-ml separating funnel and extracted with three portions (20, 10 and 10 ml) of the supporting electrolyte. These three portions were combined and transferred totally into a clean, dry cell for analysis.

For the food samples, 4.5 ml of the sample were pipetted into a 125-ml separating funnel and 0.5 ml of hydrochloric acid was added together with 25 ml of diethyl ether. The separating funnel was stoppered and shaken. The aqueous phase was discarded and the diethyl ether fraction was washed using two portions (2 ml) of distilled water. The diethyl ether layer was then back-extracted with three portions (20, 10 and 10 ml) of the supporting electrolyte. These three portions were combined and transferred totally (40 ml) into a clean, dry cell for analysis.

Determination of Salicylic Acid

The combined electrolyte was stirred using a magnetic stirrer and the voltammogram was recorded. The peak height of salicylic acid at 0.85 V was measured.

With the analyser at the "off" position, 0.5 ml of the standard solution was pipetted into the cell. The voltammogram was then recorded again. The addition of the standard solution and the recording of the voltammogram were repeated until 1.5 ml of the standard solution had been added. The amount of salicylic acid in the sample was determined by the standard additions technique.

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Result and Discussion

In selecting the solvent for extracting the analyte into the organic solvent, those solvent systems recommended by standard methods[3,6] were adopted. Therefore ethanol - diethyl ether and diethyl ether were used for the drugs and foods, respectively. The dissociation constant for salicylic acid is 1.07×10^{-3} and it dissociates completely at a pH above 5.[19] The pH of the solution used to back-extract the salicylic acid should therefore be greater than 6. To select the pH of the back-extraction solution, a known amount of the analyte was added to either diethyl ether or ethanol - diethyl ether and then extracted with aqueous solutions of different pH. The results showed that above pH 7, the extraction efficiency was >90% and a pH of *ca.* 9 (0.015 M disodium hydrogen phosphate) was therefore chosen as the working medium for extraction and voltammetric determination.

In scanning from 0.0 to 1.0 V using the glassy carbon electrode as the working electrode, two peaks (0.4 and 0.85 V) were observed for salicylic acid. The first had no analytical value because the precision was poor and the response was non-linear with respect to concentration. As a result the second peak (0.85 V) was chosen because on scanning three times at the 11.3 p.p.m. level, the relative standard deviation was 3.8%. A typical voltammogram is shown in Fig. 1.

Calibration Graph, Recovery and Precision

The calibration graph for salicylic acid was linear up to 25 p.p.m. The slope was 0.87 μA p.p.m.$^{-1}$ and gave a correlation coefficient of 0.9993. The lowest concentration of salicylic acid detected was 0.5 p.p.m.

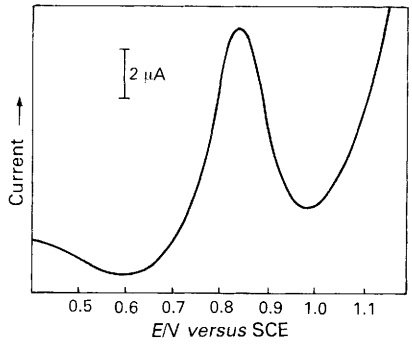

Fig. 1. Typical voltammogram of salicylic acid (9 p.p.m.)

Table 1. Interference studies; concentration of salicylic acid, 9 p.p.m.

Interferent	Concentration added, p.p.m.	Concentration of salicylic acid found, p.p.m.	Error, %
Methyl paraben . .	1.5	8.51	−5.5
Methyl salicylate . .	6.9	8.46	−6.0
Phenol	14.8	9.57	6.3
Tartrazine	15.0	9.45	5.0

The recovery and precision were studied by adding a known amount of the analyte to simple cream (3.12% *m/m*) and an apple drink (334 p.p.m.), which were free of salicylic acid and then analysed five times using the proposed procedure. The recovery was *ca.* 99% with a precision of 5%. An ointment sample was also assayed four times and gave a salicylic acid content of 7.78 ± 0.17%, which was *ca.* 97.2% of the claimed value.

Interference Studies

Various substances commonly found in drugs and foods were investigated. Voltammograms of a number of substances were scanned. Substances including boric acid, camphor, cetyl alcohol, ethanol, mercury(II) chloride, menthol, saccharin, sodium citrate, starch, sulphur, titanium dioxide and zinc oxide did not exhibit a peak within the working potential range and are therefore not expected to cause significant interference. Methyl paraben, methyl salicylate, phenol and tartrazine all exhibited peaks within the working potential range. Their concentrations that caused a 5% deviation in the peak current at 0.85 V for 9 p.p.m. of the analyte were determined. The results are summarised in Table 1. Phenol and tartrazine can be tolerated up to a 1 : 1 ratio. The method is affected by methyl paraben and methyl salicylate. However, these compounds seldom co-exist with salicylic acid and hence should not affect the determination of salicylic acid using a glassy carbon electrode.

Real Sample Analysis

The results for drug analysis using the proposed method (Table 2) are in close agreement with the claimed values and HPLC methods. The titration methods have a lower accuracy, especially for ointments D and E and prickly heat powder. In part, this can be explained by a matrix effect. Ointment D contained 30% zinc oxide and the prickly heat powder contained an appreciable amount of boric acid (4.5%). Therefore when these samples were titrated directly with standard sodium hydroxide, the interferent caused a negative deviation for ointment D and a positive deviation for the powder.

Although the spectrophotometric method is more accurate and sensitive than titration, the solvent system used was not effective enough to extract the analyte. As for ointments D and E in the first few trials, the results obtained were much lower than the claimed values. Satisfactory results could only be obtained when heat was applied to melt the ointment during the extraction.

In Hong Kong salicylic acid was once found to be added illegally to fish ball to improve its palatability.[20] This indicated the necessity to have more control over its application. As it has been banned therefore, the validity of the method could only be tested by known addition. The results (Table 3) show that the proposed method can be applied successfully to various types of food samples such as wine and oil. This is

Table 2. Drug sample analysis

Sample	Claimed value*	Concentration found*			
		Proposed method	Titration†	Spectrophotometry[8]	HPLC[14]
Ointment A	2.0	1.76	1.78	—	1.89
B	3.0	3.08	2.77	—	3.11
C	8.0	7.78	7.55	7.77	8.09
D	2.0	2.09	0.80	2.26	—
E	2.5	2.39	4.15	2.49	—
Backache pill	13.9	12.90	—	12.90	—
Prickly heat powder	0.5	0.47	0.82	0.49	—
Eye lotion	0.025	0.026	—	0.072	0.026

* Concentration is expressed as % of salicylic acid except for the backache pill, which is expressed as % of sodium salicylate.
† The BP method[6] was used for ointments A and D and the prickly heat powder and iodimetry[7] was used for the other ointments.

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Table 3. Food sample analysis

Sample	Salicylic acid added, p.p.m.	Concentration found, p.p.m. Proposed method	AOAC method[3]
Apple drink	334	329	325
Beer	171	160	174
Blackcurrant drink	148	138	151
Fish ball	277	291	250
Lemon tea	160	154	182
Orange juice	319	303	275
Peanut oil	246	244	251
Soya sauce	239	227	213
Vinegar	186	176	174
Table wine	266	271	302

much superior to the AOAC method, in which the colour development is affected by ethanol,[3] and illustrated by the analysis of the table wine. In addition, the AOAC method involves more tedious clean-up steps that are simplified in the proposed method.

Conclusion

The proposed voltammetric method is simple, specific, economical and sensitive for the determination of salicylic acid in pharmaceutical formulations and foods. Although it is not as convenient as the HPLC method, it offers the advantage that little preliminary preparative work is needed. In the HPLC method the column has to be flushed for 1–2 h before analysis and HPLC grade solvent is required for the preparation of the mobile phase; in the proposed method no such tedious work is required and the reagents are much cheaper. The HPLC method is suitable for routine work where many samples are to be analysed but when samples are to be analysed on an occasional basis, the proposed method is to be prefered as little preliminary work has to be done and no expensive solvents or reagents are required.

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