Table 2. The effect of drum rotational speed on material carryover and process efficiency (solids application rate 7·30 g min^{-1}, charge 10 kg).

Drum rotation speed rev min^{-1}	12	15	20	24
Material carryover %	1·81	1·85	2·13	2·21
Process efficiency %	98·2	98·1	97·9	97·8

Table 3. The effect of charge size on material carryover and process efficiency (solids application rate 7·30 g min^{-1}, drum speed 16 rev min^{-1}).

Charge size kg	6	10	12
Material carryover %	3·25	1·85	1·82
Process efficiency %	96·7	98·1	98·2

These results have important practical implications in the film coating of solid dosage forms and are particularly relevant to sustained release products where the drug release rate is dependent on, inter alia, the thickness and the uniformity of the film coating. In this case increasing the drum rotational speed may well be detrimental since, although improving mixing of the tablet bed, it may well result in increased carryover and decreased film thickness. The results illustrate the potential of this accurate, rapid and simple technique of isokinetic sampling of the exhaust duct in the optimization of process conditions during product development.

The authors wish to thank Professor A. I. Bailey and Dr C. Del Cerro of Imperial College and Mr J. E. Gillett of ICI Pharmaceuticals Division, for helpful discussions during this work.

REFERENCES

British Standard 3405 (1971) British Standards Institute, London

Pickard, J. F. (1979) PhD thesis. Council for National Academic Awards

Pickard, J. F., Rees, J. E. (1974) Manufacturing Chemist Aerosol News 45: 42–45

Porter, S. C. (1979) Pharm. Tech. 3: 55–59

Stairmand, C. J. (1951) Trans. Inst. Chem. Engrs. 29: 15–44

J. Pharm. Pharmacol. 1982, 34: 470–472
Communicated December 23, 1982

0022–3573/82/070470–03 $02.50/0

Determination of salicylic acid in acetylsalicylic acid by second derivative u.v.-spectrophotometry

P. Mazzeo*, M. G. Quaglia, F. Segnalini, * *Istituto di Chimica Farmaceutica e Tossicologica dell'Università, 70126 Bari, Italy, Istituto di Chimica Farmaceutica e Tossicologica dell'Università, 00185 Rome, Italy*

Salicylic acid (SA) is the major decomposition product of acetylsalicylic acid (ASA). It is well known that the free acid can cause gastric diseases; therefore several methods have been developed for its determination in ASA pharmaceutical preparations.

These methods have employed partition chromatographic (Levine & Weber 1968; Guttman & Salomon 1969), gas liquid chromatography (Galante et al 1981), liquid chromatography (Baum & Cantwell 1978), high power liquid chromatography (Ali 1976; Das Gupta 1980; Kirchhoefer 1980; Kirchhoefer & Juhl 1980), spectrophotometric (Reed & Davis 1965; Clayton & Thiers 1966), colorimetric (Kubin & Gaenshirt 1976; Juhl & Kirchhoefer 1980) and fluorometric (Shane & Miele 1970; Shane & Stillman 1971; Schenk et al 1972) procedures.

This paper reports a simple, rapid and accurate method for the direct determination of salicylic acid in ASA by second derivative u.v.-spectrophotometry. Fig. 1 shows the zero order and second derivative ultraviolet spectra of solutions of ASA, SA and ASA with SA in dioxane, and the method of measurement.

Materials and methods

Apparatus. The spectra were obtained with a Perkin-Elmer Model 200 ultraviolet-visible spectrophotometer, equipped with a Hitachi electronic derivative module. Derivative conditions: scan speed 240 nm min^{-1}; spectral slit width 2 nm; mode (time constant) No. 6; response slow.

Reagents. Salicylic acid was analytical reagent grade. Acetylsalicylic acid used for the control analytical curves was prepared by purifying the pure commercial product with ten crystallizations from anhydrous methylene chloride. Dioxane was spectroscopic reagent grade. Dry ethyl ether used for the extraction of the pharmaceutical forms was prepared by a Brockmann zero basic alumina column.

Pharmaceutical preparations analysis. The powdered pharmaceutical form was rapidly extracted with anhydrous ethyl ether at room temperature. The ether solution obtained after filtration was evaporated under reduced pressure and the residue rapidly dissolved in dioxane. The concentration of this last solution was related to the amount of SA in the sample. The second derivative of the u.v.-spectrum was registered and the peak-trough amplitude at 308 nm was

Table 1. ASA concentrations in the sample solution related to the SA concentration in the sample.

SA (ppm)	ASA (mg ml^{-1})
10–100	15
100–1000	1·5
1000–50 000	0·15

* Correspondence.

measured (a cm). The measurement was then repeated (b cm) after addition of a definite amount (for example 0·15%) of SA to the sample solution.

$$\% \text{ of SA in the sample} = 0{\cdot}15 \frac{a}{b - a}$$

Results

Control analysis. The method was verified with ASA solutions containing increasing and known amounts of free SA (from 10 to 50 000 ppm). As reported in Table 1, ASA concentration in the dioxane solutions was related to the amount of SA in the samples. This was realized in order to obtain appropriate absorbance values in the interval of wavelengths used.

Under the experimental conditions ASA, within the wide concentration range examined, does not interfere with the peak-trough amplitude relative to SA, which becomes zero when no SA is present. The graphs obtained plotting h (peak-trough amplitude in the second derivative spectrum at 308 nm) against SA concentration in the sample show a linear relationship within the considered interval (10–50 000 ppm). The relative correlation coefficients, calculated by the least-squares method, vary between 0·993 (10–100 ppm) and 0·9997 (100–2000 ppm).

Table 2 shows the results obtained in a control determination according to the previously proposed method on a standard ASA sample containing 0·075% of SA, by adding 0·15% of this acid.

Identical analytical results can be obtained by comparing the second derivative spectrum of the sample with that of a standard SA solution in dioxane.

The minimum SA concentration detectable by means of the present method in the ASA samples corresponds to 0·000 15 mg ml^{-1} (10 ppm).

To verify that ASA is not hydrolysed in the solvent used for our determination, the variation with time of the second derivative spectrum of an ASA solution (1·5 mg ml^{-1}) in dioxane, anhydrous dioxane, abs. ethanol and methylene chloride has been studied. As illustrated in Table 3, the hydrolytic degradation is negligible in dioxane solution

Table 2. Results obtained in a series of analyses of a solution (1·5 mg ml^{-1}) of ASA in dioxane, containing 0·075% of SA, by adding 0·15% of this acid. h = peak-trough amplitude in the second derivative spectrum at 308 nm.

Measure	% SA contained	h (cm)	% SA found	Error (% SA)
1	0·075	2·65	—	—
	0·075 + 0·15	8·0	0·074	−0·001
2	0·075	2·75	—	—
	0·075 + 0·15	8·05	0·078	+0·003
3	0·075	2·6	—	—
	0·075 + 0·15	7·9	0·074	−0·001
4	0·075	2·6	—	—
	0·075 + 0·15	7·9	0·074	−0·001
5	0·075	2·5	—	—
	0·075 + 0·15	7·8	0·071	−0·004

Mean value: 0·074% SA.
Error: −0·001.
Standard deviation of the mean: ±0·001.

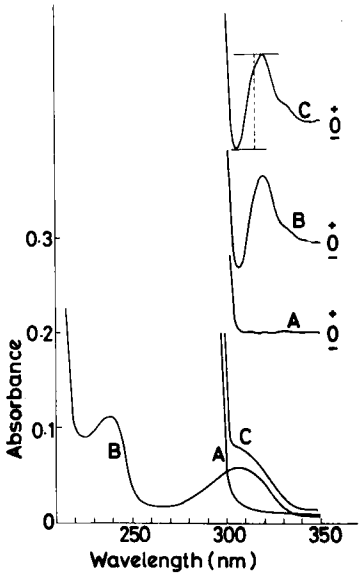

FIG. 1. Zero order (below) and second derivative ultraviolet spectra (above) of A (ASA, 1·5 mg ml^{-1} in dioxane), B (SA, 0·0015 mg ml^{-1} in dioxane), C (binary mixture of A and B). Derivative conditions: scan speed 240 nm min^{-1}; spectral slit width 2 nm; mode 6.

while it is evident in ethanol and particularly in methylene chloride, also after a short time. No difference in behaviour between dioxane and anhydrous dioxane can be detected.

Determination of SA in commercial ASA. Table 4 shows the results obtained in the determination of SA in commercial ASA (raw material and solid pharmaceutical preparations), in comparison with those given by the official USP XIX (1975) procedure.

Discussion

The methods proposed in the literature and previously reported for SA determination in ASA can be realized only by means of quite complex and time-consuming techniques. Furthermore, such methods require procedures which may increase the amount of the hydrolysed product during manipulation of the sample.

The procedure we propose is simple and rapid. Inconveniences such as hydrolysis during the determination can

Table 3. h (peak-trough amplitude in the second derivative spectrum at 308 nm) at various times for solutions (1·5 mg ml^{-1}) of ASA in dioxane, anhydrous dioxane, abs. ethanol and methylene chloride.

Solvent	h 0 min	h 20 min	h 40 min	h 60 min
Dioxane	0	0·5	0·5	0·5
Anhydrous dioxane	0	0·5	0·5	0·5
Abs. ethanol	0	3·6	10·5	16·7
Methylene chloride	0	7·1	18·2	out of scale

Table 4. Determination of SA in commercial ASA (raw material and solid pharmaceutical forms). Results are compared with the official U.S.P. XIX procedure.

Type of sample	Sample concn. (mg ml^{-1})	% SA added (mg ml^{-1})	% SA found	% SA U.S.P. method
Commercial ASA	1·5	0·0015	0·11	0·12
Commercial ASA	1·5	0·0015	0·084	0·081
Tablets	3·0	0·003	0·014	0·014
Tablets	3·0	0·003	0·016	0·016
Tablets	3·0	0·003	0·016	0·017
Tablets (microincapsulated ASA)	0·3	0·0015	0·58	0·56
Tablets (microincapsulated ASA)	0·3	0·0015	0·38	0·40
Tablets (microincapsulated ASA)	0·3	0·003	0·48	0·45

be avoided and results can be given with a high degree of accuracy and precision; furthermore no calibration curve is needed. Rather than the more usual technique based on a comparison between the second derivative spectrum of a standard solution and that of the sample, the method reported in this paper is based on the comparison of the sample solution with a reference solution containing the same substances of the sample and not only the reference product. This procedure is less time-consuming and has the same degree of accuracy and precision.

The solvent used for the determination, besides having the capacity to avoid hydrolytical degradation of ASA, shows a low volatility and good solvent properties for common excipients. It is, nevertheless, advisable to complete the determination in the minimum amount of time required for this procedure to reduce the time of solvent–solute interaction.

REFERENCES

Ali, S. L. (1976) J. Chromatogr. 126: 651–663

Baum, R. G., Cantwell, F. F. (1978) J. Pharm. Sci. 67: 1066–1069

Clayton, A. W., Thiers, R. E. (1966) Ibid. 55: 404–407

Das Gupta, V. (1980) Ibid. 69: 113–115

Galante, R. N., Egoville, J. C. Visalli, A. J. Patel, D. M. (1981) Ibid. 70: 167–169

Guttman, D. E., Salomon, G. W. (1969) Ibid. 58: 120–122

Juhl, W. E., Kirchhoefer, R. D. (1980) Ibid. 69: 544–548

Kirchhoefer, R. D. (1980) Ibid. 69: 1188–1191

Kirchhoefer, R. D., Juhl, W. E. (1980) Ibid. 69: 548–550

Kubin, H., Gaenshirt, H. (1976) Pharm. Ind. 38: 224–227

Levine, J., Weber, J. D. (1968) J. Pharm. Sci. 57: 631–633

Reed, R. C., Davis, W. W. (1965) Ibid. 54: 1533–1534

Schenk, G. H., Boyer, F. H., Miles, C. I., Wirz, D. R. (1972) Anal. Chem. 44: 1593–1598

Shane, N., Miele, D. (1970) J. Pharm. Sci. 59: 397–400

Shane, N., Stillman, R. (1971) Ibid. 60: 114–116

The United States Pharmacopeia (1975) 19th rev Mack Publishing Company, Easton Pa., p 39

J. Pharm. Pharmacol. 1982, 34: 472–473
Communicated March 1, 1982

0022–3573/82/070472–02 $02.50/0

Determination of the anhydrous morphine content of ammonium chloride and morphine mixture B.P.

KEITH HELLIWELL*, PENNY GAME, *Research and Development Laboratories, William Ransom & Son Ltd, Hitchin, Hertfordshire, U.K.*

The British Pharmacopoeial assay for the content of anhydrous morphine in ammonium chloride and morphine mixture (mistura tussi sedetiva) depends upon liquid–liquid extraction followed by colour development with nickel chloride/iodic acid reagent. This method is unsatisfactory in that it takes about 6 h to perform and produces inconsistent results (Table 1). It does, however, overcome the problem of interference from the liquorice content of the mixture, which, until recently, had prevented the application of the Radulescu type determination to liquorice containing pharmacopoeial morphine preparations (Helliwell & Sanders 1978; Helliwell & Game 1980).

A procedure is now described which overcomes this interference and allows the determination of the morphine content of ammonium chloride and morphine mixture by the method of Radulescu (1905) as modified by Adamson & Handisyde (1946). For this, four samples of the mixture were examined; one was a laboratory prepared sample and the other three were purchased from local pharmacies. The laboratory sample and one of the purchased samples were prepared from the components of the mixture, whilst the other two purchased samples were prepared by diluting commercially available concentrates.

The anhydrous morphine content was determined by the following method:

20·0 g sucrose were dissolved in 15·0 ml of the preparation with the aid of gentle heat (the temperature was maintained below 40 °C). This solution was transferred to a separator with the aid of 3 ml dilute ammonia solution (10% w/w) and 5 ml ethanol (96% v/v). The mixture was extracted with 20 ml chloroform and then with 2 × 20 ml of a 4:1 mixture of chloroform and ethanol. Each chloroform fraction, after separation, was washed, by *gentle* agitation, with the same 2 × 12 ml of a 3:1 mixture of water and ethanol. The combined chloroform fractions were evaporated to dryness on a waterbath and 5 ml M HCl added with gentle warming to dissolve the residue as completely as possible. This acid extract was transferred to a 50 ml volumetric flask with the aid of water and made to volume. To 20·0 ml of a filtered portion of this solution were added 8 ml of a freshly prepared 1·0% w/v solution of sodium nitrite in water. This mixture was allowed to stand

* Correspondence.