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First-derivative spectrophotometric determination of salbutamol in pharmaceutical preparations

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Abstract—The development of a first-order derivative spectrophotometric assay of salbutamol as a single-component and in combination with beclomethasone dipropionate in pharmaceutical formulations is described. The method eliminates the interference of tablet excipients and allows the determination of both components without their previous separation. The precision of the method for the assay of salbutamol in tablets was 1·0% with an average recovery of 98·8%. In the assay of the two-component preparation, the precision was 1·1%, with average recoveries for salbutamol of 99·3% and for beclomethasone dipropionate of 99·4%.

Derivative spectrophotometry is a fast and simple technique useful in the assay of multicomponent systems (Tobias 1983; Korany et al 1985) or single-component dosage forms in the presence of interfering excipients (Jones & Marnham 1981; Davidson & Hassan 1984). This technique was applied in the determination of salbutamol, a bronchodilator, as a single-component in tablets, salbutamol sulphate and in combination with beclomethasone dipropionate in an aerosol.

The official assay for salbutamol sulphate in tablets (British Pharmacopoeia 1988) indicates the use of an anionic ion-exchange resin to retain interfering excipients before recording the absorbance value at 276 nm.

No official procedure has been published for the quantification of salbutamol and beclomethasone dipropionate; an HPLC method has been reported by Hallworth & Westmoreland (1987). The zero-crossing technique of measurement (O'Haver & Green 1976) has been useful in the assay of binary mixtures (Morelli 1988).

Materials and methods

Apparatus. The spectra were obtained with a Beckman DU70 spectrophotometer with derivative capability (equipped with a dot matrix printer), using 1 cm silica quartz cells. The spectral slit width was 2 nm and the response time 0·05 s.

Standards. Salbutamol sulphate (Glaxo do Brazil S.A.), salbutamol and beclomethasone dipropionate (Glaxo do Brazil S.A.) were used without further purification.

Assay of salbutamol sulphate in tablets. A standard solution of salbutamol sulphate was prepared in 0·1 M HCl (ca 0·075 mg mL^{-1}).

Twenty tablets were weighed and pulverized. An accurately weighed amount of powder equivalent to 15 mg of salbutamol sulphate was placed in a 100 mL volumetric flask, and about 80 mL of 0·1 M HCl added. The powder was dissolved by shaking for 30 min or by placing the flask in an ultrasonic bath for 15 min. The volume was made up to 100 mL with 0·1 M HCl. The solution was filtered, discarding the first 10 mL of the filtrate. Five mL of the filtrate was diluted to 10 mL with 0·1 M HCl.

The first-derivative of the UV spectrum of both test and standard solutions over the range 300 to 240 nm was recorded using 0.1 M HCl in the reference cell. Suitable conditions for first derivative spectroscopy were: scan speed 60 nm min^{-1}; $\Delta\lambda$ 2 nm; ordinate settings $\pm$ 0·06. The maximum at 286 nm (Fig. 1b) was measured and mean measurements obtained for test and standard solutions were used to calculate the salbutamol sulphate contents of the tablets.

Assay of salbutamol in combination with beclomethasone dipropionate in aerosols. A standard solution of about 0·06 mg mL^{-1} of salbutamol in 95% ethanol and another containing about 0·03 mg mL^{-1} of beclomethasone dipropionate in 95% ethanol were prepared. A dose of aerosol equivalent to 3 mg of salbutamol

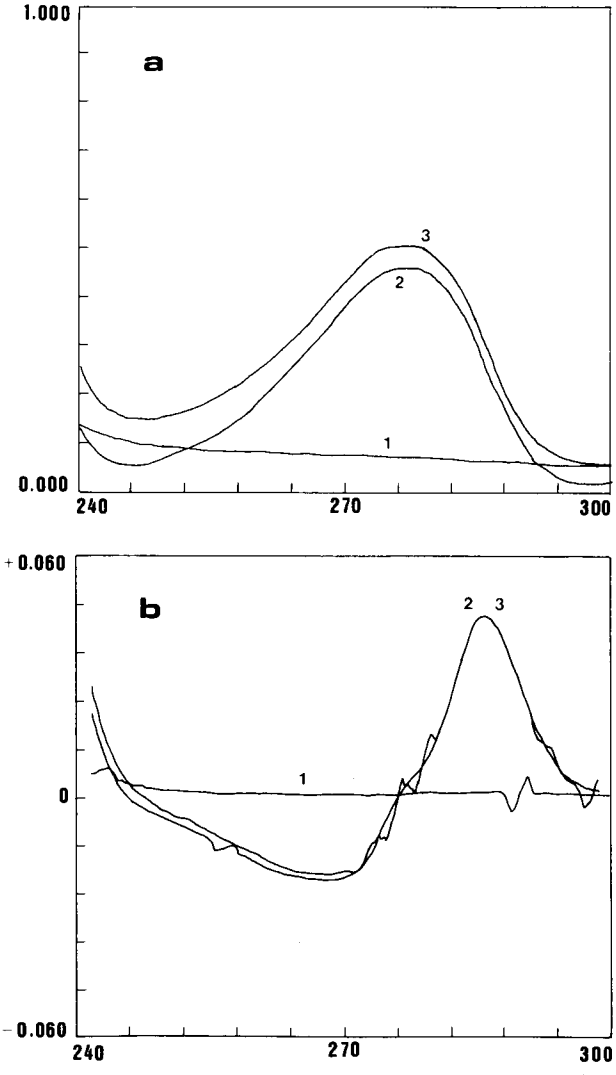

FIG. 1. Zero order (a) and first-derivative ultraviolet spectra (b) of tablet excipients in 0·1 M HCl. (1); standard solution, 0·075 mg mL^{-1} in 0·1 M HCl. (2); test solution, 0·075 mg mL^{-1} 0·1 M HCl (3).

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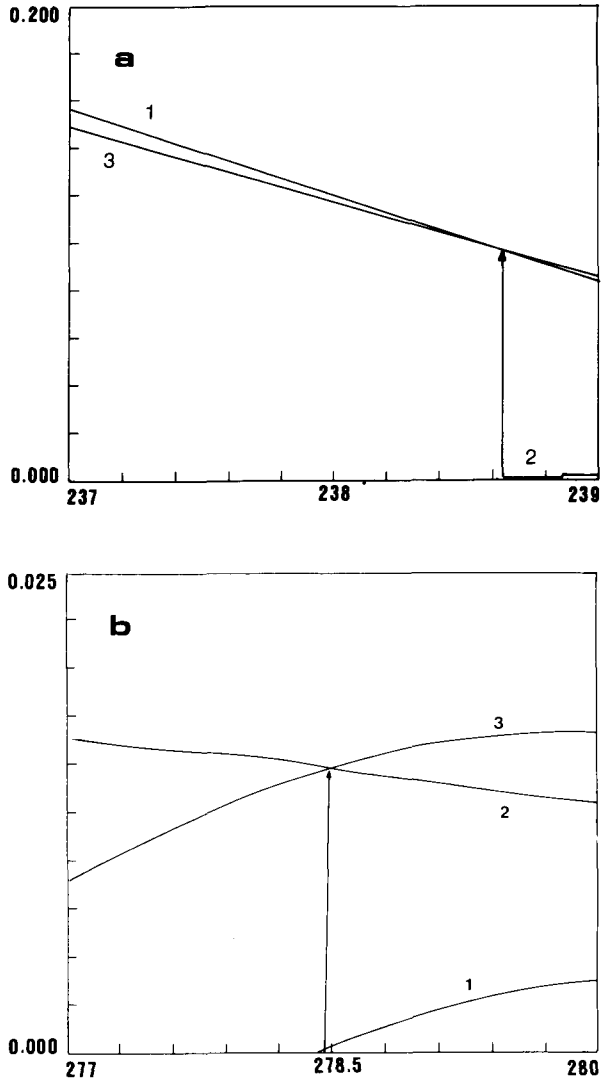

FIG. 2. First-derivative ultraviolet spectra of salbutamol, 0·06 mg mL^{-1} in 95% ethanol (1); beclomethasone dipropionate, 0·03 mg mL^{-1} in 95% ethanol (2) and binary mixture of beclomethasone dipropionate and salbutamol (3); (a) is the wavelength range for the measurement of salbutamol; (b) is the wavelength range for the measurement of beclomethasone dipropionate.

and 1·5 mg of beclomethasone dipropionate was accurately transferred to a 50 mL volumetric flask, and diluted to volume with 95% ethanol.

The first-derivatives of the UV spectra of the test and standard solutions over the range 300 to 220 nm, were recorded using 95% ethanol in the reference cell. Suitable conditions for first-derivative spectroscopy were: scan speed 60 nm min^{-1}, $\Delta\lambda$ 2 nm. Parameters were selected in order to amplify the zero crossing region of each derivative of the interfering component (Fig. 2): ordinate setting 0·000 to 0·200 and wavelength range 239 to 237 nm for salbutamol measurement at 238·6 nm; ordinate setting 0·000 to 0·025 and wavelength 280 to 277 nm for beclomethasone dipropionate measurement at 278·4 nm. Mean measurements on test and standard solutions were used to calculate the salbutamol and beclomethasone dipropionate contents of the aerosols.

Results and discussion

Linearity. The proportionality of the measured amplitude and the concentration was checked for each drug by means of a six-point calibration graph at concentrations of 0, 25, 50, 75, 100 and 125% of the analytical concentration. In all cases, a proportional relation was established, with correlation coeficients $\geqslant$0·9999 and relative standard errors of estimation $\leqslant$0·5% (Table 1).

Experimentally, the measurement selected was that which exhibited the best linear response to the analyte concentration and a zero or near zero intercept on the ordinate of the calibration graph as well as being the least affected by the concentration of any other component (Talsky et al 1978). The zero-crossing technique, chosen for the binary mixture assay is ideal in terms of systematic error, but it is more sensitive to small drifts of the band of the other component, compared with graphical measurements (O'Haver & Green 1976). Therefore, it is advisable to verify the working wavelengths by recording the derivative spectra of the single component standards before recording the test solutions.

Assay specificity. Recovery experiments were carried out as indicated by AOAC (1984). A salbutamol sulphate solution was added to mixtures of the following pharmaceutical excipients in the appropriate quantities used in tablets: dye, starch, mannitol, gelatin, polyvinylpyrrolidone, magnesium stearate. An average recovery of 98·8% was obtained for salbutamol sulphate. Mixtures of excipients without drug gave a baseline spectrum (Fig. 1a).

Recovery experiments were carried out by adding salbutamol and beclomethasone dipropionate in ethanolic solution containing sorbitan trioleate, a surfactant used to keep drugs in suspension in liquified gases. These gases are expelled during the preparation of the sample so they do not interfere in the assay. An average recovery of 99·3% for salbutamol and 99·4% for beclomethasone dipropionate was obtained (Table 2).

Table 1. Calibration and precision data for measurement of first-derivative amplitude in mm.

Calibration	Salbutamol sulphate	Salbutamol	Beclomethasone dipropionate
Quantity assayed (μg)	0–90	0–75	0–37·5
Number of solutions	8	6	6
Slope	0·6339	1·0667	2·4800
Intercept	0·1769	1·0000	−0·1000
Correlation coefficient	0·9999	1·0000	1·0000
Relative standard error of estimation (%)	0·43	0·00	0·46
Precision			
Quantity assayed (μg)	75	60	30
Number of measurements	10	10	10
Relative standard deviation (%)	A = 1·0[a] B = 0·7[a]	0·9	1·1

a: A = commercial sample, B = simulated sample.

Table 2. Recovery of standard solution added to pharmaceutical preparations*.

	Added ($\mu g\ mL^{-1}$)	Found ($\mu g\ mL^{-1}$)	Recovery (%)
Salbutamol sulphate tablets			
Sample			
Commercial	4	3·93	98·2
	8	7·86	98·2
	20	20·05	100·2
Simulated	4	3·98	99·5
	8	7·95	99·4
	20	20·28	101·4
Simulated two-component sample			
Compound			
Salbutamol	24	23·84	99·3
Beclomethasone	12	11·93	99·4

*All the results are an average of 3 assays.

Precision of analytical results. The precision of the amplitude measurements under the instrumental conditions was determined by recording the first-derivative spectra of ten drug solutions at their analytical concentrations. The relative standard deviations of the amplitudes of salbutamol sulphate, salbutamol and beclomethasone dipropionate were all in the range of 0·7–1·1%.

Comparison with the official method. To verify the efficiency of the proposed method, the concentrations of salbutamol sulphate in commercial and simulated tablets were determined by the derivative procedure and also by the procedure described in the British Pharmacopoeia 1988. The good agreement of the results obtained (Table 1) confirmed that the proposed procedure is accurate and suitable as a rapid alternative to the official method for salbutamol tablets.

No official procedure has been described and published for assay of the aerosol with two components but the results obtained by the application of the derivative procedure in simulated samples demonstrates its efficiency (Table 3).

Table 3. Data obtained in the analysis of samples using the first-derivative spectrophotometry and the official method.

Formulation	Declared strength	Found (% declared strength) BP	New method
Salbutamol sulphate tablets	2·0 mg	102·8	101·6
Salbutamol sulphate tablets	2·0 mg	100·2	101·5
Salbutamol (two-component) aerosol	0·1 mg/dose	—	101·2
Beclomethasone dipropionate (two-component) aerosol	0·05 mg/dose	—	98·3

References

Association of Official Analytical Chemists (1984) Official Methods of Analysis. 14th edn, Arlington, pp XXI

British Pharmacopoeia (1988) Her Majesty's Stationery Office, London, p. 1001

Davidson, A. G., Hassan, S. M. (1984) Assay of benzenoid drugs in tablet and capsule formulations by second-derivative ultraviolet spectrophotometry. J. Pharm. Sci. 73: 413–416

Hallworth, G. W., Westmoreland, D. G. (1987) The twin impinger: a simple device for assessing the delivery of drugs from metered dose pressurized aerosol inhalers. J. Pharm. Pharmacol. 39: 966–972

Jones, R., Marnham, G. (1981) The assay of procyclidine in tablets and injections by derivative spectrometry. Ibid. 33: 458–459

Korany, M. A., Wahbi, A. M., Mandour, S., Elsayed, M. A. (1985) Determination of certain drugs in multicomponent formulations by first-derivative ultraviolet spectrophotometry. Anal. Lett. 18(B1): 21–34

Morelli, B. (1988) "Zero-crossing" derivative spectrophotometric determination of mixtures of cepharin sodium and cefuroxime sodium in pure form and in injections. Analyst 113: 1077–1082

O'Haver, T. C., Green, G. L. (1976) Numerical error analysis of derivative spectrometry for the quantitative analysis of mixtures. Anal. Chem. 48: 312–318

Talsky, G., Mayring, L., Kreuzer, H. (1978) High-resolution higher-order UV/VIS derivative spectrophotometry. Angew. Chem. Int. Ed. Engl. 17: 785–799

Tobias, D. Y. (1983) First-derivative spectroscopic determination of acetaminophen and sodium salicylate in tablets. J. Assoc. Off. Anal. Chem. 66: 1450–1454

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Unusual solubility behaviour of cyclosporin A in aqueous media

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Abstract—The solubility of cyclosporin A was determined in water and in Sorensen buffers at pH 1·2 and 6·6 at temperatures ranging from 5 to 37°C. No differences in solubility behaviour were observed among the three aqueous media. Solubility was found to be inversely proportional to the temperature in each medium, indicating that the heat of solution was exothermic in each case.

The only oral dosage form of cyclosporin A (CyA) currently available consists of olive oil, ethanol, and polyoxyethylated oleic glycerides (Labrafil) (40:18:42) with a CyA concentration of 100 mg mL^{-1} (Tarr & Yalkowsky 1989). It is recommended that this formulation (Sandimmune) be diluted with milk, chocolate milk or orange juice immediately before administration. However, the bioavailability of CyA from this dosage form is incomplete and erratic. Problems which can be specifically associated with the dosage form include precipitation of the drug upon dilution, inaccuracy of the dose administered and lack of patient compliance. Dissolution limitations, problematic intestinal permeability and first pass metabolism during transfer through the gut wall and liver (Ueda et al 1984; Humphrey 1986; Ptachcinski et al 1986) have also been identified as potential sources of the erratic absorption behaviour. One factor which has not been considered and which may play a role in reproducibility of absorption is the solubility profile of CyA as a function of temperature. Large changes in CyA solubility with

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