ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
14 (1996) 357–362

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

*Short communication

Spectrophotometric determination of salbutamol sulphate using chlorinated quinones in the presence or absence of acetaldehyde

Rania S. Bakry, Omayma Abdel Razak, Abdel Fattah M. El Walily *, Saeid F. Belal

Pharmaceutical Analytical Chemistry Department, College of Pharmacy, University of Alexandria, Alexandria 21521, Egypt

Received for review 23 February 1995; revised manuscript received 12 June 1995

Keywords: Salbutamol sulphate; Chloranil; Dichlone; Acetaldehyde; Charge transfer; Condensation

1. Introduction

Salbutamol sulphate or albuterol sulphate, the hemisulphate of 1-(4-hydroxy-3-hydroxymethylphenyl)-2-(*tert*-butylamino) ethanol, is a direct-acting sympathomimetic with a relatively selective action on β_2-adrenoreceptors. It is used therapeutically as a potent bronchodilator [1]. The drug is official in both the USP XXIII [2] and the BP 1993 [3]. These official compendia describe non-aqueous titrations for the drug in bulk. The tablets are official only in the BP 1993, which applies a HPLC procedure for their assay. The physical and chemical characteristics of salbutamol with some references for its quantitation have been collated in an analytical profile of the drug [4].

Several colorimetric procedures have been reported based on the phenolic nature of salbutamol. Diazo coupling with different diazotized amines [5,6], formation of aqueous copper chelates [7] or blue phenol indophenol [8] and reaction with sodium cobaltinitrite [9] have been the main reactions utilized for its determination. Salbutamol sulphate (SA) has been determined in its pharmaceutical preparations using almost all the other available analytical techniques. Halogenated quinones such as 2,3,5,6-tetrachlorobenzoquinone (chloranil-(CH)) and 2,3-dichloronaphthoquinone (dichlone-(DI)) were used as π-acceptors with various electron donors to form charge-transfer complexes [10,11].

In this work, these quinones have been used to form coloured charge-transfer complexes with salbutamol base (method I). The second method (method II) used the modification of the Hamilton and Robinson reaction proposed by Buckley et al. [12] as the basis for the determination of SA. The highly coloured dialkylaminovinylquinone was formed from the reaction between one of the halogenated quinones, acetaldehyde and SA as the secondary amine. This reaction has been used for determining ephedrine and phenylephrine [13], piperazine [14] and some β-adrenergic blocking drugs [15] in their pharmaceutical preparations. These two reactions have been used in the present work as the basis of the determination of SA in tablets.

* Corresponding author.

SSDI 0731-7085(95)01609-0

Table 1
Optical characteristics and statistical data of the regression equations for charge-transfer complex formation and condensation with acetaldehyde in the presence of the chlorinated quinones in the analysis of salbutamol sulphate

Parameter	Chloranil		Dichlone	
	Without acetaldehyde	With acetaldehyde	Without acetaldehyde	With acetaldehyde
Maximum wavelength (nm)	550	660	490	570
Beer's law limits (mg per 100 ml)	10–30	2–7	5–20	3–8
Apparent molar absorpitivity ($l\,mol^{-1}\,cm^{-1}$) [a]	7.77×2	3.44×10^3	1.24×10^3	3.02×10^3
Sandell's sensitivity ($\mu g\,ml^{-1}$ per 0.001 A)	3.83×10^{-1}	8.38×10^{-2}	2.51×10^{-1}	9.40×10^{-2}
Regression equation				
Intercept (a)	-1.37×10^{-2}	-1.57×10^{-3}	-2.50×10^{-2}	8.20×10^{-3}
Slope (b)	2.70×10^{-2}	1.19×10^{-1}	4.29×10^{-2}	1.05×10^{-2}
Correlation coefficient (r)	0.9995	0.9998	0.9995	0.9998
Variance (S_0^2)	9.31×10^{-5}	1.68×10^{-4}	2.26×10^{-4}	1.15×10^{-4}

[a] Calculated on the basis of the molecular mass of salbutamol sulphate.

2. Experimental

2.1. Apparatus

Absorbance measurements were made on a Perkin-Elmer Model 550S double-beam UV–visible spectrophotometer attached to a Hitachi Model 561 recorder, with a fixed slit-width of 2 nm and 1 cm matched quartz cells.

2.2. Materials and reagents

All chemicals were of analytical-reagent grade unless specified otherwise. Salbutamol sulphate was kindly supplied by Pharco Pharmaceutical (Alexandria, Egypt) as a gift and was certified to contain 99.40%. Tablets were purchased locally. Chloranil and dichlone (Aldrich Chemical, Milwaukee, WI, USA) were prepared as 1% solutions in acetone. A 10% (v/v) solution of acetaldehyde (Merck, Darmstadt, Germany) in propan-2-ol was used.

Stock salbutamol sulphate solution

A 0.5 mg ml^{-1} solution was prepared by dissolving the appropriate amount of standard drug in a suitable volume of dimethylformamide (DMF); heating in boiling water-bath was necessary to dissolve the powder.

2.3. General procedures and calibration graphs

Method I

Appropriate volumes of solutions prepared from the standard drug solution, in the concentration range stated in Table 1, were placed in 5 ml volumetric flasks. The solutions were diluted to constant volume with DMF. For the reaction with CH, 0.7 ml of the reagent was added and the flasks were allowed to stand at 60°C for 10 min in a thermostated water-bath. For DI, 2 ml of reagent were added and the flasks were heated for 30 min at 60°C. In both cases, the solutions in the flasks were diluted to volume with DMF and the absorbance values of the solutions were recorded at the maximum wavelength stated in Table 1 against simultaneously prepared blanks.

Method II

Appropriate volumes of the standard solution in the concentration range stated in Table 1 were placed in 5 ml volumetric flasks. The solutions were diluted to a constant volume with DMF (1.0 ml). To each flask, 0.4 or 0.5 ml of 1% (w/v) CH or DI solution, respectively, was added followed by 0.9 or 0.5 ml of 10% (v/v) acetaldehyde solution in the case of CH or DI, respectively. The flasks were heated for 10 min at 60°C, cooled and diluted to volume with propan-2-ol. The absorbance was measured against a simultaneously

prepared blank at the specified wavelengths (Table 1).

2.4. Procedure for the assay of the tablets

Twenty tablets were weighed and an accurately weighed amount of the finely powdered tablets equivalent to about 10.0 mg of SA was transferred into a 25 ml volumetric flask. The flask was half-filled with DMF and 0.5 g of activated charcoal was added (in the case of pink tablets); the flask was heated in a boiling water-bath for 20 min. The solution was cooled and diluted to volume with the same solvent. The solution was filtered and the first few millilitres of the filtrate were discarded. different aliquots from the filtrate were measured by pipette and the method was continued as mentioned under the general procedure for the two reactions.

3. Results and discussion

3.1. Method I

The reaction of SA with CH and (DI) results in the development of violet to orange–red solutions which exhibit absorption maxima at 555 and 590 nm, respectively. The colours can be attributed to the formation of charge-transfer complexes between SA as the n-donor and the halogenated quinones (CH and DI) as π-acceptors.

$$D^{\cdot\cdot} + A \rightarrow [D^{\cdot\cdot}\text{–}A] \rightarrow D^{+} + A^{-}$$

The above suggestion was confirmed by the absence of a reaction between SA as salt and the chlorinated quinones due to the presence of the nitrogen in the protonated form. Belal et al. [10] and Abou Ouf et al. [11] converted the analysed drugs into the free base by using ammonia or sodium hydrogen carbonate, respectively. In the present work and because SA base is water soluble, the drug base was set free by using DMF as solvent.

3.2. Method II

In this method, the basic secondary nitrogen of SA base in DMF was condensed with acetaldehyde to give an enamine derivative. The enamine formed acted as a nucleophile and condensed with the halogenated quinones to form a blue dialkylaminovinylquinone. The reaction was based on the work of Buckly et al. [12] and had been utilized for the quantitation of some drugs containing a free secondary amine group in their molecular structures [13–15].

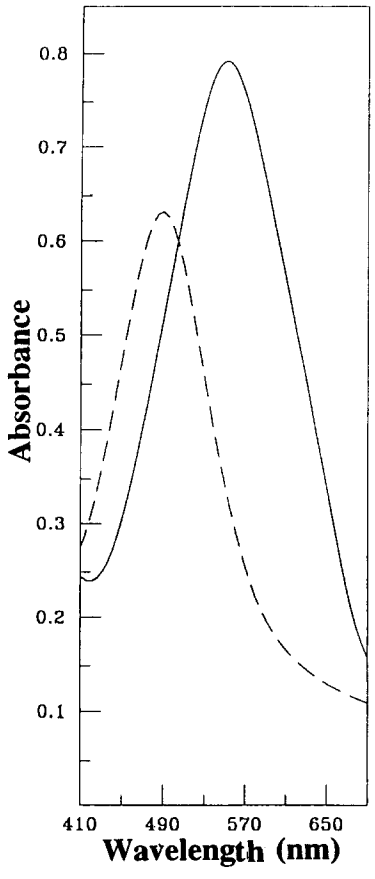

Fig. 1. Absorption spectra of the coloured chromophores formed through the reaction of 15 and 30 mg per 100 ml SA with DI (dashed line) and CH (solid line), respectively.

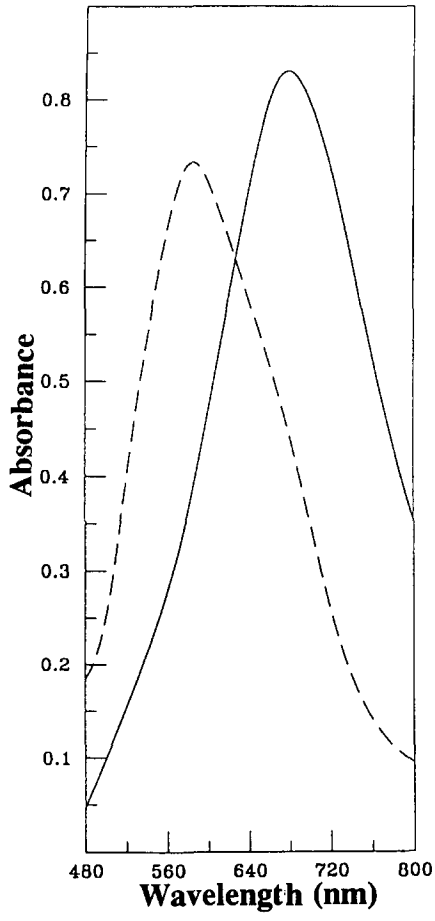

Fig. 2. Absorption spectra for the reaction product of 7 mg per 100 ml SA with DI (dashed line) or CH (solid line) in the presence of acetaldehyde solution.

3.3. Optimum reaction conditions

Figs. 1 and 2 show the absorption spectra of the reaction products of SA and halogenated quinones in the absence and presence of acetaldehyde. Both reaction conditions were optimized by changing one factor and keeping the rest constant.

Method I

The most suitable volumes of 1% solutions of CH and DI were found to be 0.7 and 2 ml, respectively. The optimum reaction time and temperature for maximum sensitivity were found to be 10 and 30 min at 60°C for CH and DI, respec-

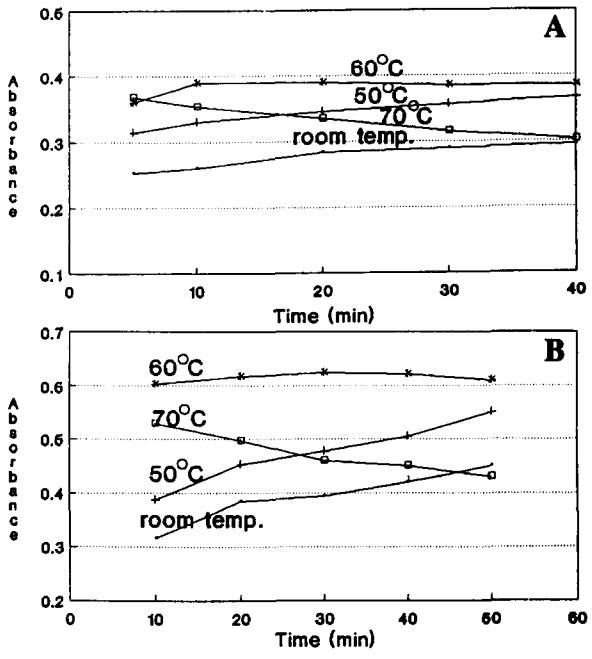

Fig. 3. Effects of temperature and heating time on the formation of 15 mg per 100 ml SA complex with (A) CH and (B) DI.

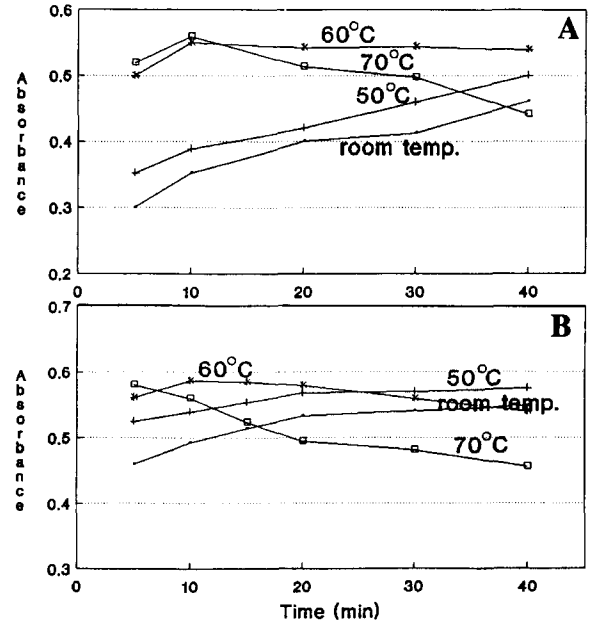

Fig. 4. Effects of temperature and heating time on the condensation reaction of 5 mg per 100 ml SA with (A) DI and (B) CH in the presence of acetaldehyde solution.

Table 2
Application of charge-transfer complex formation and condensation with acetaldehyde in the presence of the chlorinated quinones in the analysis of commercial products containing salbutamol sulphate

Sample	Found (%) (Mean ± SD) [a]				
	Chloranil		Referee method of BP 1993	Dichlone	
	Without acetaldehyde	With acetaldehyde		Without acetaldehyde	With acetaldehyde
Ventolin tablets [b] (Batch No. 31708B)	98.38 ± 0.52	98.45 ± 0.43	98.59 ± 0.97	98.75 ± 0.63	99.05 ± 0.71
	$t = 0.43$	0.29	(2.31) [c]	0.30	0.84
	$F = 3.48$	5.01	(6.39) [c]	2.39	1.86
Farcolin tablets [b] (Batch No. 154)	96.27 ± 0.61	96.35 ± 0.55	96.29 ± 0.54	96.02 ± 0.67	96.15 ± 0.57
	$t = 0.07$	0.18		0.71	0.40
	$F = 1.27$	1.05		1.55	1.13
Salbovent tablets [b] (Batch No. 2007003)	96.69 ± 0.63	97.02 ± 0.33	97.08 ± 0.60	96.98 ± 0.69	97.57 ± 0.42
	$t = 1.00$	0.19		0.25	1.48
	$F = 1.08$	2.32		1.30	2.03
Bronchovent tablets [b] (Batch No. 128042)	101.57 ± 0.75	101.48 ± 0.97	101.09 ± 0.57	100.91 ± 0.84	101.32 ± 0.82
	$t = 1.49$	0.96		0.41	0.52
	$F = 1.12$	1.53		2.17	2.06
Salbolin tablets [b] (Batch No. 134073)	99.65 ± 0.75	99.54 ± 0.97	99.55 ± 0.81	99.50 ± 0.41	99.89 ± 0.58
	$t = 0.20$	0.02		0.12	0.76
	$F = 1.17$	1.43		3.90	1.95

[a] Mean of five determinations ± standard deviation. The results represent the percentage recovery from the label claimed amount.
[b] Ventolin tablets were manufactured by Glaxo Egypt (El Salam City, Egypt), under licence from Glaxo Group (UK). Farcolin tablets were manufactured by Pharco Pharmaceutical (Alexandria, Egypt). Salbovent tablets were manufactured by The Alexandria Co. for Pharmaceuticals and Chemical Industries (Alexandria, Egypt). Bronchovent tablets were manufactured by Misr Co. for Pharmaceutical Industries (Cairo, Egypt). Salbolin tablets were manufactured by The Arab Drug Company (Cairo, Egypt).
[c] Values in parentheses are the theoretical values at $p = 0.95$.

tively (Fig. 3A and B). Acetone and DMF were examined as diluents for the reaction. The latter gave a higher absorbance and better stability. For both CH and DI the colours produced under the above-mentioned conditions were found to be stable for at least 1 h.

Method II

Volumes of 0.9 or 0.5 ml of 10% acetaldehyde solution in propan-2-ol were found to be optimum when used with CH or DI, respectively. An excess concentration of acetaldehyde showed a negative effect on the developed colour. Volumes of 0.4 and 0.5 ml of CH and DI were found to be optimum for colour development. For both reagents, the time and temperature required for maximum colour development were found to be 10 min at 60°C (Fig. 4A and B). The effects of different solvents on the absorbance of the colour formed were studied using DMF, acetone, ethanol, propan-2-ol and dioxane. Propan-2-ol gave the highest absorbance where CH was used as the reagent; both propan-2-ol and acetone gave the same sensitivity in the case of DI. The colours produced from the reaction of CH or DI with SA in the presence of acetaldehyde were stable for at least 30 min. Under the described experimental conditions the graphs obtained by plotting absorbance at the specified wavelengths against the concentration were found to be linear over the Beer's law ranges given in Table 1.

3.4. Assay of tablets

The proposed methods were applied to the determination of salbutamol sulphate in tablets (Table 2). The results obtained by the two methods were in good agreement with those given by the official procedure since the calculated t and F values did not exceed the theoretical values. The good agreement of the results indicates the suitability of these spectrophotometric methods for the determination of salbutamol sulphate in tablets. In addition, the use of these spectrophotometric procedures leads to considerable savings in cost and time.

References

[1] J.E.F. Reynolds (Ed.), Martindale—The Extra Pharmacopoeia, Pharmaceutical Press, London, 30th edn., 1993, p. 1255.
[2] United States Pharmacopeia, XXIII Revision, United States Pharmacopeial Convention, Mack, Easton, PA, pp. 38–39.
[3] British Pharmacopeia 1993, H.M. Stationery Office, London, 1993, pp. 585 and 1092.
[4] H.Y. Aboul-Enein, A.A. Al Badr and S.E. Ibrahim, in K. Florey (Ed.), Analytical Profiles of Drug Substances, Vol. 10, Academic Press, New York, 1981, p. 665.
[5] R.T. Sane, V.G. Nayak and V.B. Malkar, Talanta, 32 (1985) 31.
[6] N. Geeta and S. Baggi, Microchem. J., 39 (1989) 137.
[7] P.K. Chartherjee, C.L. Jain and P.D. Sethi, Indian Drugs, 23 (1986) 635.
[8] D.M. Singbal and S.D. Naik, Can. J. Pharm. Sci., 16 (1981) 65.
[9] A.M. Wahbi, H. Abdine, M.A. Korany and M.H. Abdel-Hay, J. Assoc. Off. Anal. Chem., 61 (1978) 1113.
[10] S. Belal, M.A. El-Sayed, M.E. Abdel Hamid and H. Abdine, J. Pharm. Sci., 70 (1981) 127.
[11] A.A. Abou Ouf, A.M. Taha and M.B. Saidhom, J. Pharm. Sci., 62 (1973) 1700.
[12] D. Buckley, H.B. Henbest and P. Slade, J. Chem. Soc., (1957) 4891.
[13] M.M. Amer, A.M. Taha, S.R. El-Shabouri and P.Y. Khashaba, J. Assoc. Off. Anal. Chem., (1982) 894.
[14] M.B. Sidhom, J. Pharm. Pharmacol., 24P (suppl.) (1983) 35.
[15] M.A. Korany, M.H. Abdel-Hay, S.M. Galal and M.A. El-Sayed, J. Pharm. Belg., 40 (1984) 178.