ELSEVIER

Il Farmaco 57 (2002) 267–271

IL FARMACO

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Simple spectrophotometric determination of cinnarizine in its dosage forms

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Received 13 June 2001; accepted 18 December 2001

Abstract

A direct, extraction-free spectrophotometric method has been developed for the determination of cinnarizine in pharmaceutical preparations. The method is based on ion-pair formation between the drug and three acidic (sulphonphthalein) dyes; namely bromocresol green (BCG), bromocresol purple (BCP) and bromophenol blue (BPB) which induces an instantaneous bathochromic shift of the maximum in the drug spectrum. Conformity to Beer's law enabled the assay of dosage forms of the drug. Compared with a reference method, the results obtained were of equal accuracy and precision. A more detailed investigation of the cinnarizine–BCG ion pair complex was made with respect to its composition, association constant and free energy change. In addition, this method was also found to be specific for the analysis of cinnarizine in the presence of some of the co-formulated drugs, such as pyridoxine hydrochloride and digoxin. © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.

Keywords: Cinnarizine; Acid dyes; Spectroscopy; Pharmaceutical preparations

1. Introduction

Cinnarizine, (E)-1-(diphenylmethyl)-4-(3-phenylprop-2-enyl) piparizine, is a cerebral blood flow improver. It is widely used orally for the treatment of cerebral apoplexy, cerebral arteriosclerosis and post-traumatic cerebral symptoms. It is also used for the control of nausea and vomiting [1].

Cinnarizine is official, as bulk, in European Pharmacopoeia [2], which describes a non-aqueous titration for its assay. Monitoring of cinnarizine in biological fluids has been carried out mainly by HPLC with UV [3] or fluorescence detection [4]. In pharmaceutical preparations, cinnarizine was assayed by different methods including GC [5], HPLC [6–8] HPTLC [9], electrochemical [10–12] and spectrophotometric methods [12–17]. Studies of the stability of cinnarizine were also carried out spectrophotometrically [18].

The well-established spectrophotometric method is ion-pair extraction. In this case, an ion-pair is formed between basic compounds and an anionic dye such as bromophenol blue, bromocresol green, methyl orange, etc. At a specific pH, the ion-pair is extracted into an organic solvent, which is immiscible with water, and the concentration of the resulting ion pair in the organic phase is determined spectrophotometrically [19–21]. The ion-pair extraction technique has some difficulties and inaccuracies arising from incomplete extraction or the formation of emulsions between the hydrocarbon solvent and the basic compound—containing solution. In response to the problems resulting from extraction of the ion-pair, few articles were published for the analysis of pharmaceutical compounds through ion-pair formation without extraction [22–24].

This paper describes, for the first time, the application of acidic dyes to the spectrophotometric determination of cinnarizine. The formed ion-pair requires no extraction step and is measured directly in chloroform. The proposed method is applied successfully for the determination of cinnarizine either pure or in dosage forms with good accuracy and precision. Interference from some commonly co-formulated substances is also studied.

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0014-827X/02/$ - see front matter © 2002 Published by Éditions scientifiques et médicales Elsevier SAS.
PII: S0014-827X(02)01204-1

2. Experimental

2.1. Apparatus

Pye Unicam PU 8800, UV–Vis Spectrophotometer (Philips) using 1.0-cm quartz cells.

2.2. Materials and reagents

1. Cinnarizine pure sample was kindly provided by Janssen Pharmaceutica, NV, Beerse, Belgium. Stugeron tablets and Stugeron–Forte capsules labeled to contain 25 and 75 mg cinnarizine each, respectively, were obtained from commercial sources.
2. Acidic dyes; bromocresol green (BCG), bromocresol purple (BCP) and bromophenol blue (BPB), (BDH Chemicals Ltd.). Solutions were prepared as 1×10^{-3} M in chloroform.

Standard solution of cinnarizine was prepared by dissolving 10.0 mg in 100 ml of chloroform and further diluting as appropriate.

2.3. Procedures

2.3.1. Recommended procedure and calibration curve

Transfer aliquot volumes of cinnarizine solution, so that the final concentration is in the range stated in Table 1. Add suitable volume of the dye solution (Table 1). Mix and complete to volume with chloroform. Measure the absorbance of the resulting colored solutions at the specified wavelength (Table 1) against a reagent blank similarly treated.

2.3.2. Procedure for commercial dosage forms

Transfer weighed amounts of powdered commercial pharmaceutical dosage forms (tablets or capsules) equivalent to 20 mg cinnarizine into a 100-ml volumetric flask. Shake with about 50 ml of chloroform for 30 min. Complete the flask with the same solvent. Filter and proceed as under Section 2.3.1. Determine the nominal content of the tablets or capsules either from the calibration curve or using the corresponding regression equation.

3. Results and discussion

3.1. Absorption spectra

Cinnarizine features a piperazine ring. This structure suggests the possibility of utilizing anionic dyes as chromogenic reagent. In chloroform, cinnarizine is not an absorbing species in the visible region. Also, the dyes used have almost negligible absorbance (Fig. 1). In contrast, when a solution of BCG, BCP or BPB in chloroform is added in a large excess to the drug solution, an intense yellow color is immediately produced (Fig. 1). This is due to the conversion of the dye into an open quinonoidal anionic derivative [19], which forms an ion-pair with cinnarizine.

3.2. Reaction conditions

The experimental conditions were studied and it was found that 0.5 ml of BPB and 2 ml of either BCG or BCP were sufficient to produce maximum and reproducible color. The formed colors were stable for at least 1 h.

3.3. Investigation of the cinnarizine-BCG ion-pair complex

The composition of the ion-pair complex formed between cinnarizine and BCG (as a model example of

Table 1
Optical characteristics and statistical data of the regression equations for the cinnarizine reaction with bromocresol green, bromocresol purple and bromophenol blue

Item	BCG	BCP	BPB
Volume of the dye (ml)	2	2	0.5
λ_{max} (nm)	414	414	404
Beer's law limit (μg/ml)	2–10	1–10	1–8
Apparent molar absorptivity (l/mol per cm)	1.85×10^4	3.36×10^4	2.9×10^4
Sandell's sensitivity (μg/ml per 0.001 A)	0.0198	0.0109	0.0127
Regression equation			
Intercept (a)	–0.022	–0.054	–0.016
S_a	4.70×10^{-4}	3.74×10^{-4}	3.15×10^{-4}
Slope (b)	0.0503	0.0912	0.0788
S_b	7.76×10^{-5}	5.72×10^{-5}	5.88×10^{-5}
Correlation coefficient (r)	0.9996	0.9999	0.9999
Detection limit in (μg/ml)	0.63 (1.7×10^{-6} M)	0.68 (1.8×10^{-6} M)	0.29 (7.8×10^{-7} M)

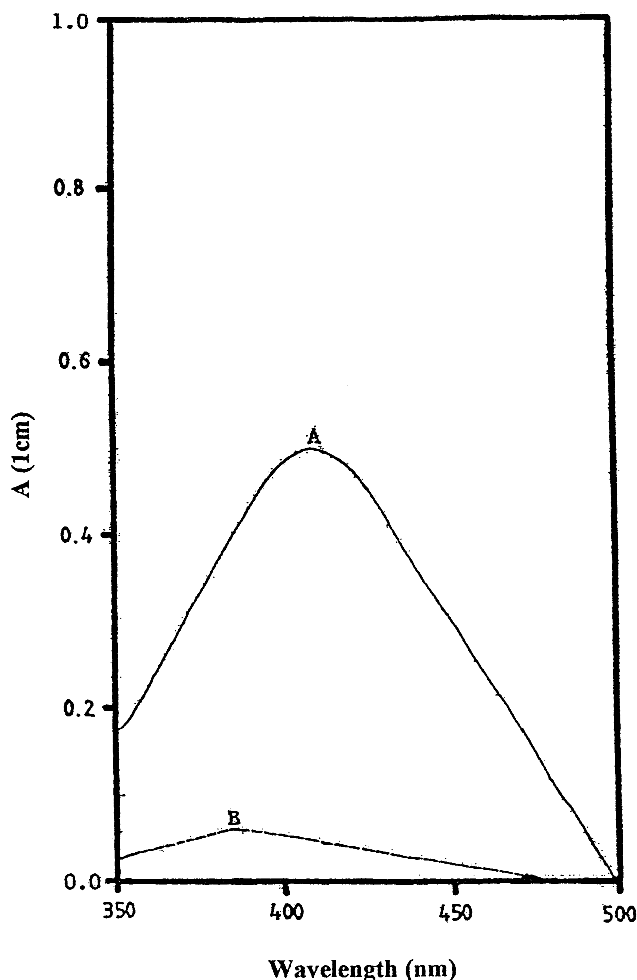

Fig. 1. Absorption spectrum of the reaction product of cinnarizine 10 μg/ml and BCG 2×10^{-4} in chloroform. A, reaction product. B, blank.

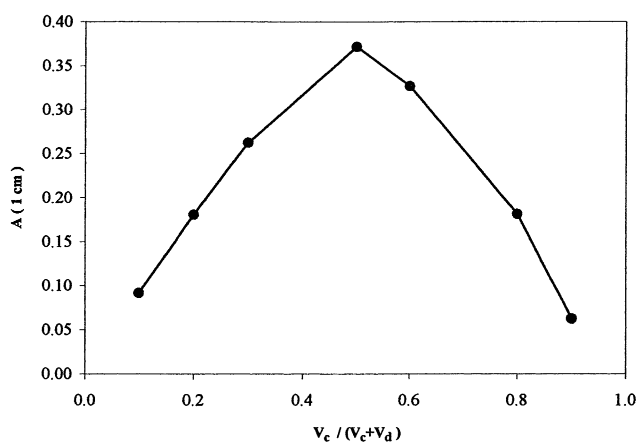

Fig. 2. Continuous variation plot for cinnarizine–BCG (2×10^{-4} M) complex ratio (V_c, V_d are the volumes of cinnarizine and BCG, respectively).

the used dyes) was established by Job's method of equimolar solutions [25] which indicated a 1:1 ion-pair ratio (Fig. 2). The result was confirmed by means of the limiting logarithmic method [26]. The two straight lines obtained either upon using increasing concentrations of the drug while keeping the concentration of the dye (BCG) constant, or upon using increasing concentrations of the dye while keeping the drug concentration constant, gave a straight line with a slope of 0.974 and 1.11, respectively, i.e. the molar ratio of the reaction is 0.974:1.11, i.e. 1:1.

Using Job's method, the stability constant (K) of the ion-pair formed between the drug and BCG was found to be 7.3×10^2. The standard free energy change ΔG [27] was related to the association constant and calculated to be -5.27 kcal. The negative value of ΔG point out to a spontaneous reaction.

3.4. Analytical performance

3.4.1. Linearity of the method

Under the above experimental conditions, linear correlations were obtained between the absorbance and cinnarizine concentration over the range stated in Table 1 with good correlation coefficients and small intercepts. The apparent molar absorptivities Sandell's sensitivities and detection limits [28] were summarized in the same table.

3.4.2. Specificity and interference studies

Formation of the ion-pair complex with anionic dyes needs a basic drug; therefore, no possible interference is expected from other co-formulated drugs lacking any basic center such as digoxin.

Also, the proposed methods were applied to the determination of cinnarizine in combination with pyridoxine hydrochloride; a co-formulated drug. The results revealed that no interference from pyridoxine hydrochloride was detected. Pyridoxine hydrochloride, will not interfere because it is not extractable with chloroform. Any co-formulated drug, which is not extractable with chloroform will not interfere in the assay.

It was also shown that tablet and capsule excipients, such as talc, lactose, maize starch, avisil, hydrogenated vegetable oil and magnesium stearate did not interfere with the assay.

3.4.3. Precision and accuracy

Statistical analysis of the regression equations allowed the calculation of standard deviation of the intercept (S_a), standard deviation of the slope (S_b) and standard deviation of the residuals ($S_{y/x}$). The small values of these parameters indicate the high precision of the proposed method [28] (Table 2).

In order to determine the accuracy and the precision of the method, standard solutions containing three different concentrations of cinnarizine were analyzed in five replicates. The mean results obtained are

Table 2
Application of the proposed spectrophotometric methods to the determination of cinnarizine in pure form

Proposed method				Official method [2]
Conc. taken (μg/ml)	% Recovery [a]			% Recovery [a]
	BCG	BCP	BPB	
2	99.80	99.77	101.01	
4	99.15	100.00	98.40	
6	101.92	99.53	100.07	
8	98.58	99.16	100.27	
$\bar{X}$	99.86	99.62	99.94	99.66
SD	1.46	0.36	1.10	0.73
t	0.25 (2.31)	0.10 (2.31)	0.42 (2.31)	
F	4.00 (5.39)	4.11 (4.13)	2.27 (6.39)	

The figures in parentheses are the tabulated values of t and F at $P = 0.05$.
[a] Mean of five determinations.

summarized in Table 3. The small values of the standard deviation (SD), the relative standard deviation (RSD%) and the mean standard analytical error (SAE) can be considered adequate for the quality control analysis of pharmaceutical preparations.

Table 3
Evaluation of the accuracy and precision of the proposed method for cinnarizine determination

Dye	Cinnarizine (μg/ml)		SD	RSD%	SAE
	Added	Found [a]			
BCG	2	2.00	0.021	1.050	9.39×10^{-3}
	4	4.02	0.031	0.771	1.39×10^{-2}
	6	6.01	0.041	0.682	1.83×10^{-2}
BCP	2.0	1.998	5.07×10^{-2}	2.537	2.27×10^{-2}
	4.0	4.010	3.42×10^{-2}	0.852	1.53×10^{-2}
	8.0	8.002	2.49×10^{-2}	0.311	1.11×10^{-2}
BPB	1.0	1.003	9.55×10^{-3}	0.952	4.27×10^{-3}
	2.0	2.008	1.92×10^{-2}	0.956	8.59×10^{-3}
	4.0	4.000	2.24×10^{-2}	0.560	1.00×10^{-2}

[a] Mean for five determinations.
SD, standard deviation; RSD%, relative standard deviation; SAE, standard analytical error.

The proposed method was applied to the determination of pure sample of cinnarizine. The results obtained by the proposed methods were compared with those given by the official method [2]. Application of the t- and F- tests [28] showed that there was no significant difference in the precision and accuracy between the two methods (Table 2).

3.5. Pharmaceutical applications

Table 4 shows the results obtained for the determination of cinnarizine in commercial tablets and capsules by means of both the proposed methods and a reference method [13]. The proposed methods are equally accurate and precise as the reference method as indicated by the t- and F- tests, respectively. Tablets and capsules excipients, such as talc, lactose, maize starch, avisil, hydrogenated vegetable oil and magnesium stearate, did not interfere with the assay.

4. Conclusion

The proposed methods are rapid, simple, accurate and in addition, offer advantages in determining

Table 4
Application of the proposed spectrophotometric method to the determination of cinnarizine in dosage forms

Commercial product	% Recovery [a] ± SD			Reference method [13]
	BCG	BCP	BPB	
Stugeron tablets (25 mg of cinnarizine/tablet)	99.6 ± 0.35	99.7 ± 0.38	100.2 ± 0.26	99.9 ± 0.21
t	1.47	0.92	1.80	
F	2.78	3.27	1.53	
Stugeron–Forte capsules (75 mg of cinnarizine/capsule)	100.0 ± 0.23	99.9 ± 0.4	99.5 ± 0.31	99.7 ± 0.25
t	1.77	0.85	1.00	
F	1.18	2.56	1.54	

The theoretical values of t and F at $P = 0.05$ are 2.31 and 6.39, respectively.
[a] Mean of five determinations.

cinnarizine, (in pharmaceutical preparations), when extraction difficulties arise with other spectrophotometric methods. These advantages encourage the application of the proposed methods in routine quality control of cinnarizine even in presence of some co-formulated drugs.

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