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DETERMINATION OF ASTEMIZOLE BY A SPECTROPHOTOMETRIC CHARGE- TRANSFER METHOD

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ABSTRACT

Iodine-astemizolc charge-transfer complex has been utilized for the assay of astemizolc. The *complex* formed in the proposed mcl hod shows strong absorption at 360 rim with a corresponding molar absorptivity. ε, of 3.26 x 10^4 L mof^l cm and obeyance of Beer's law over the concentration range. 2-12 pg/ml. When the proposed method was applied to commercial tablets labeled to contain 10 mg of active ingredient per tablet, the mean percentage !blind was 99.72 ± 1.36. Analysis of variance, (ANOVA), and added recovery experiments indicated adequate precision and accuracy for the method.

Introduction

Astemizole, 1-[(4-f1uorophenyl)methyl]-N-[1-(4-methoxyphenyl)-ethyl]-4-piperidinyl-lH-benzimidazol-2-amine (Fig.1), is a second generation anti-histamine (Bussche, et al. 1984) characterized by having high affinity for III-receptor, long duration of action and non-sedative side effects.

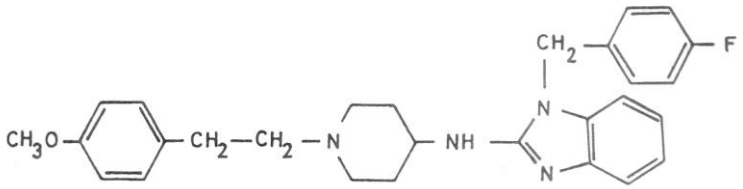

Fig. 1

Relatively few methods are reported for the determination of astemizole. These include radiommunoassy (Woestenborghs, et al. 1986) and high-performance liquid chromatography, HPLC, (Woestenborghs, et al. 1983) for the drug and its metabolites in plasma and animal tissues. A reversed-phase HPLC method (Sadana and Potdar, 1989) was described for the assay of astemizole in pharmaceutical dosage forms.

In this report a new simple spectrophotometric method based on el-wage-transfer complex formation with iodine has been developed for the quantitation of astemizole. The proposed method yields a strongly light-absorbing complex of λ_{max} 360 nrn and subsequently less interference is expected to originate in excipients. Furthermore, (ANOVA), coefficient of variation and results of added recovery experiments suggest that the proposed method is adequately precise and accurate.

Experimental

Apparatus

Varian DMS 90 double beam UV-Visible Spectrophotometer wish 1-cm quartz cells.

Materials

Reference substance (R 43512) of astemizole kindly received from Janssen Pharmaceutica, Turnhoutseweg-30, B-2340 Beerse, Belgium, was used without further treatment. The tablets employed (Batch No.90F16/161) were purchased from local pharmacies in Riyadh, Saudi Arabia.

Reagents

0.5% w/v Iodine in dry chloroform was prepared.

Standard solution

About 10 mg of reference astemizole was accurately weighed and dissolved in 100 ml dry chloroform.

Sample preparation

Twenty tablets were accurately weighed and powdered. A quantity of powder containing 10 mg astemizole was dissolved as completely as possible in 20 ml chloroform; the admixture was filtered into a 100 ml calibrated-flask. The residue was extracted further with 3 x 20 ml chloroform and the volume was adjusted to 100 ml.

Calibration curve

Aliquot portions 2-12 ml of standard astemizole solution were transferred to 100 ml

volumetric flask and 5 ml of iodine solution was added to each. The solutions were mixed, each was completed to 100 ml with dry chloroform and finally kept aside for 25 minutes. The absorbances were measured at 360 nm against appropriate blanks prepared similarly.

Assay

To 6 ml of the sample solution in 100m1 volumetric flask 5 ml of iodine solutions was added and the volume was adjusted to the mark dry chloroform. The solution was set a side for 25 minutes and the absorbance was read at 360 nm against appropriate blank. The concentration of the drug was determined from the standard curve. Alternatively the concentration could be computed from an equivalent linear regression equation.

Results and Discussion

The theory and applications of complexation by charge-transfer mechanism, ($n \rightarrow \pi$), were reported by several investigators (Popvo and Rugg, 1957, Foster, 1969, Henry, et al. 1977, Feigl, 1966, Al-Sulimany and Townshead, 1973, Al-Ghabsha, et al. 1976 and Lin and Cheng, 1980). Upon addition of iodine to astemizole indry chloroform, the violet colour of iodine changed to yellowish purple. The drug could be regenerated by extraction with aqueous hydrochloric acid and the violet colour of iodine was restored in the chloroform layer. These findings implied the formation of a weak complex between iodine and astemizole.

To utilize the formation of the complex for the assay of astemizole, the absorption spectra of iodine-astemizole mixtures were scanned in UV-Visible region (Fig. 2). A relatively strong absorption band emerged with Amax at 360 nm. The absorbance of iodine solution was 0.06 while that of astemizole in chloroform was negligible at 360 nm (Fig. 2). The optimum conditions established for the formation of the complex were 5 ml of 0.5% w/v iodine in chloroform and 25 minutes to complete the reaction.

To study the stiochiometry of the complexation reaction, the continuous variation method (lob, 1928) was adopted. Fig. 3 indicates to a good approximation a molar ratio of 1:4 (astemizole:iodine). No attempts were made to study further the mechanism of the reaction.

Table I summarizes the results obtained using the experimental optimum conditions. Beer's law was observed over the concentration (C) of 2-12 µg/ml astemizole and the linear equation obtained by regression analysis was $(A_1\ cm)_{360} = 0.005 + 0.069C$, correlation coefficient, r, being 0.9999 at n =6, indicating excellent linearity.

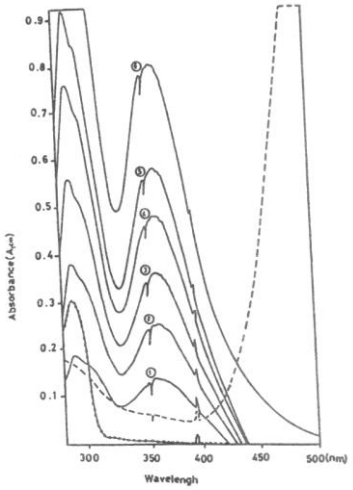

Fig. 2: UV-Visible spectra of astemizole-iodine charge-transfer complex. (1), (2), ... (6) stand for : 2, 4... 14 µg/ml astemizole (—), 0.025% iodine (------) and 12 mg/ml astemizole (-----), all in chloroform.

The small positive intercept in the equation might be due to intermolecular complexes leading to positive deviation from Beer's law (Wahbi, et al. 1986).

When the present method was applied tablets labelled to contain 10 mg astemizole, the mean percentage found was 99.72 ± 1.36 (six separate determinations, Table I). For the added recovery experiments, the corresponding mean percentage found was 99.70 ± 0.67. The relative standard deviations (or coefficients of variation) for the declared and spiked concentrations (Table I) were acceptable.

The analysis of variance (Table II) for six independent repeated measurements conducted for three consecutive days yielded a calculated F-ratio of 1.143401. At the probability of a = 0.05, the theoretical F-ratio at $df_1 = 2$ and $df_2 = 15$ is 3.68. It can be inferred that using the proposed method for the assay of astemizole, the variation from day to *day* is not significantly different from the analytical error displayed within days.

Based on the finding that the astemizole-iodine mixture absorbs strongly at 360 nm ($e=3.26 \times 10^4 L\ mol^{-1}$), the proposed method can he used satisfactorily for the quantitation of astemizole. Furthermore, absorbance measurement at 360 nm minimizes the interference, if any, of UV-absorbing excipents and impurities. The (ANOVA) carried out (Table II) and the results assembled in Table I, indicate that the proposed method is adequately precise and accurate.

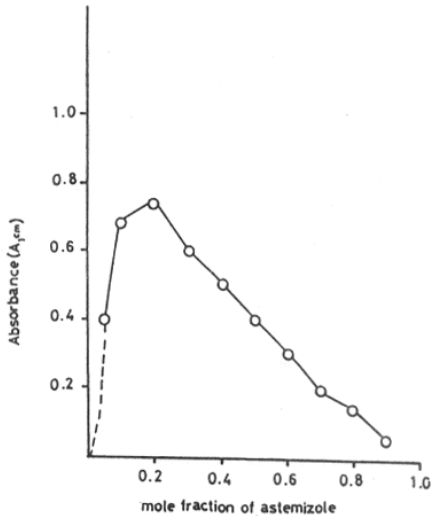

Fig. 3: Continuous variation method plot for astemizole-iodine charge-transfer complex.

Table I
Determination of astemizole tablets by charge transfer complexation with iodine**

Spectrophotometric data	Declared conc.*	Percentage found ± S.D.	Spiked conc.* + declared conc.*	Percentage recovered
Linear regression equation $(A_{1\ cm})_{360\ nm}$ = 0.005 + 0.069C n = 6, r = 0.0000. Apparent molar absorptivity ε = 3.26 x 10^4 L mol^{-1} cm^{-1}	2	97.3	4 + 2	100.8
	4	99.2	4 + 4	100.2
	6	101.8	4 + 6	99.2
	8	100.5	4 + 8	99.3
	10	99.6	6 + 6	99.0
	12	99.9	8 + 4	99.4
	Mean:	99.72	Mean:	99.70
	S.D.:	1.36	S.D.:	0.67
	R.S.D.:	1.36	R.S.D.:	0.67

*Concentration in μg/ml.
**Labeled to contain 10 mg aztemizole per tablet.

Table II
The analysis of variance (ANOVA)

Source of variation	Degrees of Freedom (df)	Sum of squares	Mean square	F-ratio
Among days	2	6.21605	3.108025	1.43401
Within days	15	40.77344	2.718229	
Total	17	46.98949		

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References

Al-Ghabsha, T.S., Rahim, S.A., Townshead, A. (1976). Spectrophotometric Determination of Microgram Amounts of Amines with Choranil. *Analytical Chim. Acta*, **85**: 189.

Al-Sulimany, F., Townshead, A. (1973). Spectrophotometric Determination of Microgram Amounts of Amino-acids with Chloranil. *Analytica Chim. Acta*, **66**: 193.

Bussche, V.G., Rombout, N. and Gijpen, L. (1984). Clinical Activity of Astemizole (Review). Medicine Publishing Foundation, Beerse, Belgium.

Bussche, V.G., Rombout, N. and Moens, M. (1984). Astemizole in Physcophysical Performance. Lack of Central and Sedative Effects. Pharmatheraputica, **3**: 3.

Feigl, F. (1966). In: "Spot Tests in Organic Analysis", 7th Edition, Elsevier, Amsterdam, pp.249, 407.

Foster, R. (1969). In: "Organic Charge-Transfer Complexes', Academic Press, Lon-don, p.313.

Henry, S.I.T., Eric, D.G., Anthony, S.D. 91977). Sensitive Assay Procedure for Ethambutol Hydrochloride via Charge-Transfer Complex Formation. J. Pharm. Sci., 66: 767.

Job, P. (1928). Ann. Chim., 9: 113. Chem. Abstr., 22: 2120.

Lin, B.Y. and Cheng, K.L. (1980). Spectrophotometric Study of Chloranil Charge-Transfer Complexes of Aminoacids and Related Compounds. Analytica Chim. Acta,

120: 335.
Popvo, A.I. and Rugg, R.H. (1957). Studies of the Chemistry of Halogens and Polyhalides. XI. Molecular Complexes of Pyridine, 2- picoline and 2, 6-lutidine with Iodine and Iodine Halides. J. Am. Chem. Soc., 79: 4622.
Sadana, G.S. Potdar, A.J. (1989). HPLC Determination of Astemizole in Pharmaceutical Dosage Forms. Indian Drugs, 27(2). 140.
Wahbi, A.M., El-Obeid, H.A. and Gad-Kariem, E.A. (1986). Spectrophotometric Determination of Diethylcarbamazine Citrate via Charge-Transfer Complex. IL Farmaco, Ed. Pr. 41(6): 210.
Woestenborghs, R., Embrechts, L., Heykants, J. (1983). Simultaneous Determination of Astemizole and its Demethylated Metabolite in Animal Plasma and Tissues by HPLC. J. Chromatogr. Biomed. Appli., 278: 359.
Woestenborghs, R., Geuens, I., Michiels, M., Hendriks, R., Heykants, J. (1986). Radiommunoassay Procedures for Astemizole and Metabolites in Plasma. Drug Dev. Res., 8(1-4): 63.