Zagazig J. Pharm. Sci., June 1997
Vol. 6, No. 1, pp. 71-76.

ISSN 1110-5089

UTILITY OF CERTAIN π-ACCEPTORS FOR THE SPECTROPHOTOMETRIC DETERMINATION OF THE ANTIHISTAMINICS TERFENADINE AND ASTEMIZOLE

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ABSTRACT

Two simple, rapid, accurate and sensitive spectrophotometric methods were described for the determination of the antihistaminics, terfenadine (I) and astemizole(II). The methods were based on the reaction of each of terfenadine and astemizole as π-electron donors with either tetrachloro-p-benzoquinone(p-chloranil, CL) or tetrabromo,1,2-benzoquinone(TBBQ) as π-acceptors, to give highly colored radical anions. The colored products with terfenadine exhibited maximum absorption at 550 nm and 573 nm with CL and TBBQ, respectively. While astemizole exhibited maximum absorption at 561 nm with CL and 578 nm in case of TBBQ. Different assay parameters have been optimized to achieve maximum sensitivity and accuracy for determination of terfenadine and astemizole. Linear relationships between absorption and concentrations have been obtained over the range of 0.05 - 1.00 mg mL^{-1} of (I) and (II). The mean percentage recoveries from triplicate determinations of nine concentrations lied in the same range of each drug were 99.45 ± 0.902 S D with CL and 99.776 ± 0.781 S D with TBBQ in case of terfenadine and 99.99 ± 0.168 S D with CL and 100.113 ± 0.284 S D with TBBQ in case astemizole. The method has been applied for the determination of terfenadine and astemizole in their tablets. The results obtained were in a good agreement with those obtained by the use of some reported procedures.

INTRODUCTION

Terfenadine (I), α-(p -tert-Butylphenyl)-4- (hydroxy diphenylmethyl)-piperidinebutanol is a distinct peripheral H_1 -receptor antagonist. Generally, terfenadine alone or in combination with pseudoephedrine is indicated for the relief of symptoms associated with seasonal allergic rhinitis[1].

Different analytical procedures for the determination of terfenadine have been reviewed[2]. Other reported procedures for the determination of terfenadine include non-aqueous titration[3-4], UV[3,5] and colorimetric[6-8] spectrometry, TLC[3,9], HPLC[10-25], GC-MS[26] procedures. Radio[27] and fluoro[28]-immunoassay procedures have been also applied for the determination of terfenadine.

Astemizole(II),1-(p-fluorobenzyl)-2-[(1-(p-methoxy phenethyl)-4-piperidylamino] benzimidazole, is a long-acting, non-sedating antihistamine which has a major clinical implications for the treatment of different allergic diseases[29].

Also, different analytical procedures for the determination of astemizole have been reviewed[29]. Other reported methods include spectrophotometric[30-31], TLC[32] and HPLC[33-34] procedures.

In the present work, a spectrophotometric methods for the determination of terfenadine(I) and astemizole(II) have been developed using π-acceptors p-chloranil(CL) and tetrabromo,1,2-benzoquinone (TBBQ). The proposed procedures were successfully applied for the determination of terfenadine and astemizole either in pure or dosage forms with good accuracy and precision. The results were compared with those given by some other reported methods.

EXPERIMENTAL

Apparatus : Shimadzu UV-160 A spectrophotometer

Materials :

Terfenadine was kindely donated by Squibb Company, Cairo, Egypt. Astemizole was kindely donated by Sedico Company, Cairo, Egypt. Tetrachloro-p-benzoquinone, p-chloranil (CL) and Tetrabromo1,2-benzoquinone(TBBQ) from BDH. Dimethylformamide and acetonitrile from Merck. All other chemicals were of analytical grade.

Pharmaceutical Preparations:

Histadine tablets (each tablet contains 60 mg of terfenadine, Amoun Pharmaceutical Industries Co., Egypt) and Triludan tablets (each tablet contains 60 mg terfenadine, Marion Merrell Dow Ltd). Hismanal tablets (each tablet contains 10 mg astemizole, Janseen) and Astemizole tablets (each tablet contains 10 mg of astemizole, Sedico, Cairo, Egypt).

Reagents and Solutions :

CL Solution : 3.5 mg mL^{-1} in acetonitrile.

TBBQ Solution : 2.5 mg mL^{-1} in acetonitrile.

Standard Drug Solutions :

Stock solutions were prepared in dimethylformamide (DMF) to contain 100 mg mL^{-1} of each of terfenadine or astemizole. Aliquots of these stock solution were diluted with DMF to give concentrations ranging from 0.05 to 1 mg mL^{-1} of each drug.

Assay Solutions for Terfenadine Tablets and Astemizole Tablets :

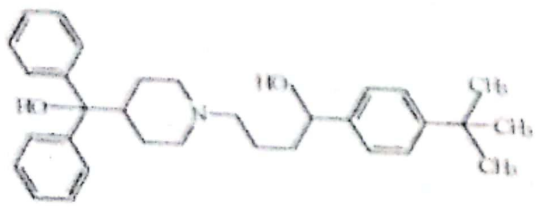
Five tablets of each brand of tablets containing terfenadine and fifteen tablets containing astemizole were weighed and finely powdered. A quantity of the powdered tablets equivalent to 100 mg of terfenadine

or astemizole was extracted with two successive portions of DMF each of 25 mL. The combined DMF extract was filtered into 100 mL volumetric flask and the volume was completed with the same solvent. Aliquots of this solution were diluted with DMF to produce 0.5 mg mL^{-1} terfenadine or astemizole solutions and used as the assay solutions.

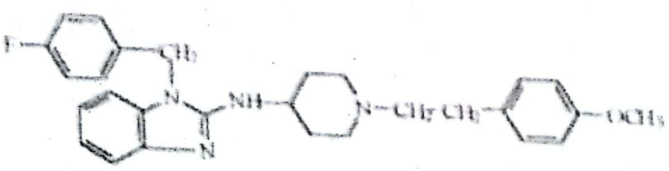
Procedure : Two mL of each drug standard solutions and the assay solutions were transferred into a 10 mL screw-capped test tubes. Two mL of either CL or TBBQ solutions were added. The mixtures were allowed to stand at room temperature for about 20 minutes in case of CL and 15 minutes in case of TBBQ. The absorbances of the resulting solutions were measured at 550 nm and 573 nm for CL and TBBQ, respectively, in case of terfenadine and at 561 nm and 578 nm for CL and TBBQ, respectively in case of astemizole, against a reagent blank experiment. Concentrations of (I) and (II) were calculated from the corresponding calibration graph prepared simultaneously.

RESULTS AND DISCUSSION

Terfenadine (I) and astemizole (II) solutions in DMF were found to yield intense colors with p-chloranil (CL) and tetrabromo-1,2-benzoquinone (TBBQ) in acetonitrile, most probably due to the formation of charge transfer complexes, because these reagents are known as π-acceptors[35]. Figure (1) shows the absorption spectra of the colored products formed with the wavelength of maximum absorption (λmax) at 550 nm for CL and 573 nm for TBBQ in case of terfenadine and 561 nm for CL and 578 nm for TBBQ in case of astemizole.



(I)



(II)

In DMF, terfenadine and astemizole yielded with each CL and TBBQ solution in acetonitrile intense purple colors. The predominant chromogens are the purple anions $CL^{\bullet-}$ and $TBBQ^{\bullet-}$ with CL and TBBQ, respectively. These colored anions were probably formed by the dissociation of an original donor-acceptor (DA) complex with terfenadine or astemizole.

$$D^{**} + A \longrightarrow \underset{\text{(DA complex)}}{D^{**}\text{-}A} \xrightarrow{\text{polar solvent}} \underset{\text{(radical ions)}}{D^{\bullet+} + A^{\bullet-}}$$

The dissociation of the (DA) complex is promoted by the high ionizing power of the solvent mixture DMF and acetonitrile. Several solvents have been tried like methanol, ethanol, 1,2 dichloroethane and dichloromethane but optimum intensity of the color were obtained with using acetonitrile for the reagents and DMF for drugs. Benzene and chloroform were unsuitable because of the limited solubility of the reagents in these solvents.

The effect of CL or TBBQ concentrations was also studied where maximum color intensity was obtained upon using 3.5 mg mL^{-1} CL solution and 2.5 mg mL TBBQ solution (Figure 2). Higher concentrations of reagents did not affect color intensity. Heat affected negatively the intensity of the produced color, accordingly the reaction was performed at room temperature. The optimum reaction time was studied by measurement of the intensity of the produced color after different periods of time at room temperature. Complete color development was achieved after 20 and 15 minutes for CL and TBBQ, respectively (Figure 3). The color remained stable for one hour in all the studied cases.

The relative sensitivities of the two acceptors were determined by comparing the molar absorpitivities (ε) of the chromogens (Table 1). TBBQ exhibited the most color intensity.

Under the above optimized conditions, linear relationships between absorption and concentrations of terfenadine (I) and astemizole (II) after reaction with each of CL and TBBQ were obtained over the range of 0.05-1.00 mg mL^{-1} for CL and TBBQ. The good linearity of the method was indicated by the regression analysis (Table I).

The mean percentage recoveries from triplicate determinations of nine concentrations lied in the same range of each drug were 99.45 ± 0.902 S D with Cl and 99.776 ± 0.781 S D with TBBQ in case of terfenadine and 99.993 ± 0.168 S D with CL and 100.113 ± 0.284 S D with TBBQ in case astemizole (Table 2).

The method has been applied for determination of terfenadine and astemizole in their tablets. The results were compared with those obtained by assaying the same dosage forms by some reported procedures[3,39] (Table 3).

From the accuracy, precision and sensitivity of the results, the method can be recommended for determination of terfenadine and astemizole in their tablets.

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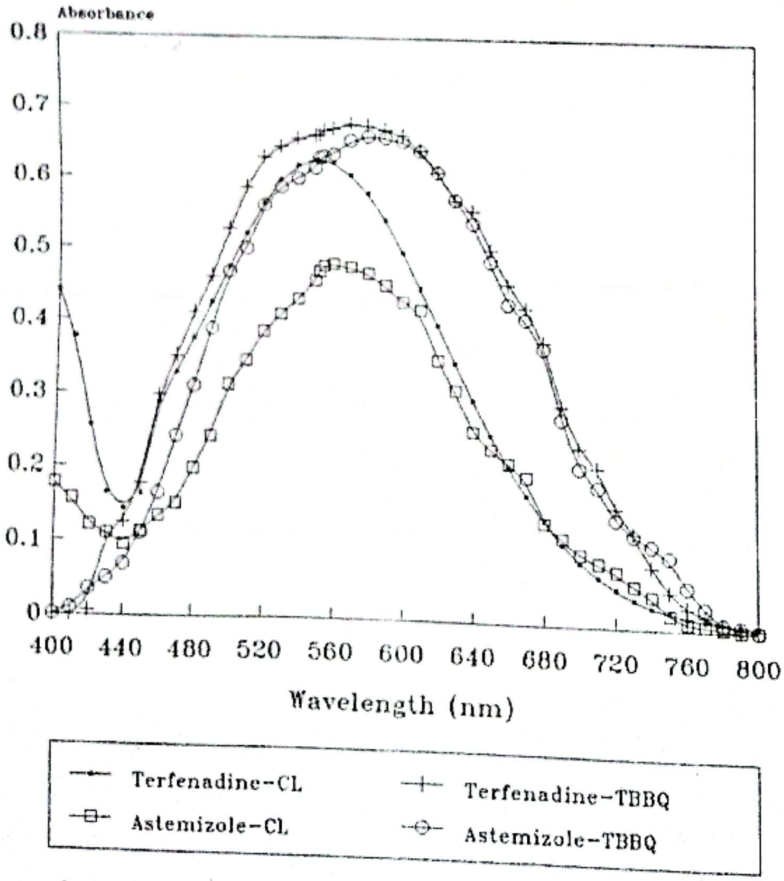
Table (1) : Analytical Parameters For The Spectrophotometric Determination of Terfenadine and Astemizole.

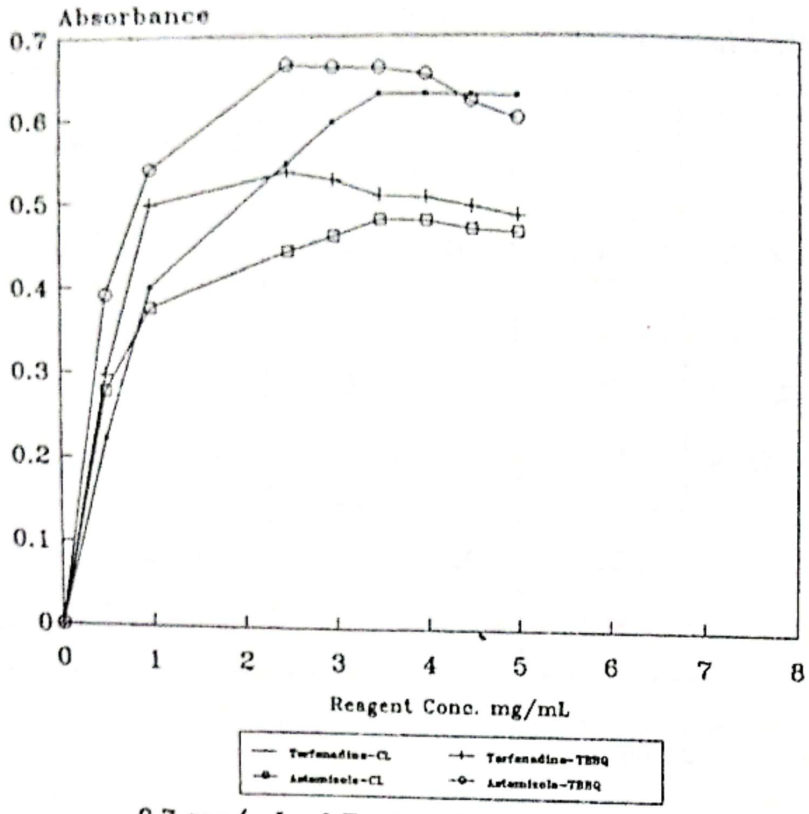
Drug**	π-Acceptor	λ_{Max} nm	Molar Absorptivity (ε)	Linear Regression Equation*		
				Intercept (a)	Slope (b)	Corr. Coeff (r)
Terfenadine	CL	550	385985	0.0395	0.8183	0.9996
	TBBQ	573	453185	0.0908	0.9606	0.9980
Astemizole	CL	561	302120	0.1323	0.6593	0.9946
	TBBQ	578	435646	0.1339	0.9507	0.9905

* Y = a + bc where Y is the absorption and c is the concentration mg mL^{-1}
** Concentration range = 0.05 - 1.00 mg mL^{-1} in all cases



0.7 mg/mL of Terfenadine or Astemizole

Fig. (1) : Absorption Spectra of, Terfenadine-CL, Terfendine -TBBQ, Astemizole-CL and Astemizole-TBBQ.



0.7 mg/mL of Terfenadine or Astemizole

Fig. (2): Effect of CL or TBBQ Conc. on the Absorption of the Reaction Product With Each of Terfenadine and Astemizole.

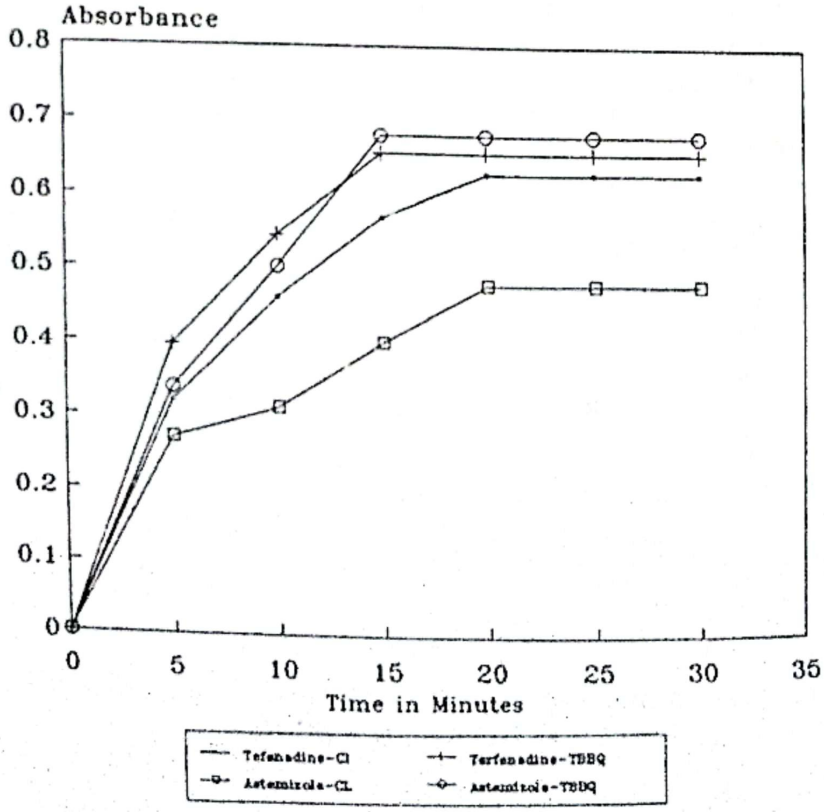


Fig. (3): Effect of Time on the Absorption of the Reaction Product of CL and TBBQ With Each of Terfenadine and Astemizole.

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Table (2): Results Of Recovery Experiments Of Terfenadine and Astemizole.

	Terfenadine				Astemizole			
	CL		TBBQ		CL		TBBQ	
Added Conc. mg mL^{-1}	Found* mg mL^{-1}	% Recovery	Found* mg mL^{-1}	% Recovery	Found* mg mL^{-1}	% Recovery	Found* mg mL^{-1}	% Recovery
0.1	0.099	99.00	0.0980	98.00	0.0997	99.70	0.0999	99.900
0.2	0.197	98.50	0.1979	98.95	0.1998	99.90	0.2009	100.45
0.3	0.296	98.67	0.2999	99.97	0.3001	100.03	0.2998	99.933
0.4	0.403	100.75	0.4009	100.23	0.4007	100.18	0.3997	99.925
0.5	0.502	100.40	0.5008	100.16	0.5001	100.20	0.4989	99.780
0.6	0.601	100.17	0.6018	100.30	0.5987	99.783	0.6007	100.12
0.7	0.699	99.857	0.7005	100.07	0.7003	100.04	0.7010	100.14
0.8	0.796	99.50	0.8020	100.25	0.8004	100.05	0.8008	100.10
0.9	0.884	98.22	0.9005	100.06	0.9005	100.06	0.9060	100.67
Mean % Recovery		99.452		99.776		99.993		100.113
± S. D.		±0.902		±0.782		±0.168		±0.284

* Mean of three determinations and calculated from the corresponding regression equation (Table 1).

Table(3): Determination of Terfenadine and astemizole in Their Tablets Using the Proposed Method and Some Reported Methods[3,30]

Brand Name (Producer)	Labeled Conc. (Drug)	% Recovery* ± S.D. t : 2.31 (p = 0.05). F : 6.39 (p = 0.05)		
		Proposed Method - CL	Proposed Method-TBBQ	Reported Method**
Histadine tablets (Amoun)	60 mg / tablet (Terfenadine)	100.36 ± 0.674 t = 1.402 F = 1.473	100.06 ± 0.656 t = 0.930 F = 1.580	99.62 ± 0.820
Triludan tablets (Marion)	60 mg / tablet (terfenadine)	98.56 ± 0.975 t = 1.341 F = 1.642	99.59 ± 0.782 t = 0.492 F = 1.051	99.83 ± 0.760
Hismanal (Janssen)	10 mg / tablet (Astemizole)	98.943 ± 0.765 t = 1.262 F = 1.581	99.864 ± 0.521 t = 0.579 F = 2.830	99.601 ± 0.876
Astemizole (Sedico)	10 mg / tablet (Astemizole)	102.543 ±0.763 t = 1.703 F = 3.129	101.956 ±0.673 t = 0.221 F = 2.435	101.877±0.431

*Mean of five determinations

**The results of analysis of the tablet forms were compared to those obtained by the use of some reported procedures for analysis of the tablets. Terfenadine tablets were assayed spectrophotometrically according to the method of Badwan *et al* [3]. In case of astemizole tablets the colorimetric method of Qquershi *et al*[30] was utilized.

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Received: Feb. 11, 1997
Accepted: April 22, 1997

أستخدام بعض الكواشف من نوع مستقبلات بيتا لتعيين مضادي الحساسية التيرفينادين والاستيمازول بطريقة طيفية

مختار محمد مبروك
قسم الكيمياء التحليلية – كلية الصيدلة – جامعة طنطا – طنطا – مصر

يصف هذا البحث طريقة طيفية بسيطة, سريعة, دقيقة و حساسة لتعيين كل من عقاري التيرفينادين والاستيمازول المضادين للحساسية. وتعتمد الطريقة علي تفاعل كل من التيرفينادين والاستيمازول كواهبين للالكترونات مع كل من رباعي كلورو بارا بينزوكينون (١) و رباعي برومو او٢ بينزوكينون (٢) من نوع مستقبلا ت بيتا حيث تنتج مركبات ملونة امكن قياس شدة امتصاصها عند اطوال موجة قصوي ٥٥٠ نم و٥٦١نم في حالة استخدام الكاشف الاول (١) مع كل من التيرفينادين والاستيمازول علي الترتيب اما في حالة استخدام الكاشف الثاني (٢) فقد تم قياس شدة امتصاص الالوان الناتجة عند اطوال موجة ٥٧٣نم و٥٧٨نم في حالة التيرفينادين والاستيمازول علي التوالي. وقد تمت دراسة كافة ظروف التفاعل وضبطها للحصول علي اعلي حساسية , حيث امكن الحصول علي علاقة خط مستقيم بين شدة الامتصاص وتركيزات مختلفة من كل عقار باستخدام كل كاشف في مدي يقع بين ٠٫٥ومج لكل مل و امج لكل مل. وقد تم تطبيق الطريقة بنجاح في تحليل بعض الاشكال الصيدلية التي تحتوي علي تلك الادوية وتمت مقارنة النتائج بنتائج تحليل نفس الاشكال بطرق اخري معتمدة حيث تم الحصول علي نتائج متقاربة.