ELSEVIER

Journal of Pharmaceutical and Biomedical Analysis
18 (1999) 985–992

JOURNAL OF
PHARMACEUTICAL
AND BIOMEDICAL
ANALYSIS

Determination of astemizole, terfenadine and flunarizine hydrochloride by ternary complex formation with eosin and lead(II)

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Received 11 November 1997; received in revised form 16 March 1998; accepted 27 March 1998

Abstract

A simple and sensitive spectrophotometric method has been established for the determination of astemizole(I), terfenadine(II) and flunarizine hydrochloride(III) based on ternary complex formation with eosin and lead(II). The method does not involve solvent extraction. The colour of the produced complex is measured at 547.5 nm for (I) and (III), while (II) is measured at 540.7 nm. Appropriate conditions were established for the colour reaction and for the eosin: Pb(II): drug ratio to obtain maximum sensitivity. Under the proposed conditions, the method is applicable over concentration range of 4.1–37.6, 11.8–47.2 and 2.4–19.1 μg ml^{-1} with mean percentage recovery of 99.20 ± 0.63, 99.76 ± 0.39 and $99.60 \pm 0.47\%$ for (I), (II) and (III), respectively. The suggested method was applied for determination of (I), (II) and (III) in pharmaceutical preparations. Through the use of a non-ionic surfactant (methylcellulose), prior extraction of the drugs was unnecessary. The results obtained demonstrated that the method is equally accurate, precise and reproducible as the official or reported methods. For the purpose of enhancing the sensitivity, a fluorescence quenching method for determination of the studied drugs via ternary complex formation was also investigated. The detection limit for the studied drugs (I), (II) and (III) was 0.94–7.1 μg ml^{-1} with mean percentage recovery of 99.84 ± 0.29, 99.24 ± 0.36 and $99.34 \pm 0.26\%$, respectively. The results obtained by applying the proposed methods were statistically analyzed and compared with those obtained by official or reference methods. Unlike other reported ion-pair techniques, the suggested methods have the advantage of being applicable for the determination of the three drugs in their pharmaceutical dosage forms without prior extraction. They are recommended for quality control and routine analysis where time, cost effectiveness and high specificity of analytical techniques are of great importance. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Spectrophotometry; Fluorometry; Ternary complex; Eosin; Lead(II); Astemizole; Terfenadine; Flunarizine hydrochloride

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PII S0731-7085(98)00107-1

1. Introduction

Astemizole(I), terfenadine(II) and flunarizine hydrochloride(III) are widely used antihistamincs. In addition, flunarizine has vasodilator effect.

Several methods have been reported for determination of (I), (II) and (III) including HPLC [1], non-aqueous titrimetry [2] colorimetry [2], UV [2] and GC [2] for astemizole; non-aqueous titrimetry [3], UV [4], colorimetry [5,6], densitometry [7] and HPLC [8,9] for terfenadine; and UV [10,11], colorimetry [12], GC [13] and HPLC [14] for flunarizine hydrochloride.

The ion-pair complex formation technique between organic dyes and different organic compounds is one of the methods available for determination of organic compounds. Suitable organic dyes including bromothymol blue, bromophenol blue, bromocresol green, methyl orange, tropaeolin O, eosin and zincon [15] are used. In addition to their lower sensitivity, these methods are complicated as extraction procedures are required due to the formation of water-insoluble complexes. The addition of a surfactant or water-miscible solvents to avoid any extraction procedure usually causes decomposition of the formed ion-pair complexes leading to impossibility of the determination.

The purpose of this study was to determine the three drugs in their pharmaceutical preparations without prior extraction by simple, rapid and selective assays for quality control and routine analysis purposes based on ternary complex formation between the studied drug–metal ion [Pb(II) $(drug)_n$] as cation and an organic dye (eosin) as anion.

2. Experimental

2.1. Apparatus

1. SHIMADZU 1601 PC UV Spectrophotometer, using quartz cell ($1 \times 1 \times 3$ cm), slit width 2.0 nm.
2. SHIMADZU RF-540 Spectrofluorophotometer, using quartz cell($1 \times 1 \times 4.5$ cm), slit width 2.5 nm.
3. Digital pH meter, Pw 9409 Pye Unicum.

2.2. Material

2.2.1. Pure samples

1. Astemizole, working standard, kindly supplied by Pharco, Cairo, Egypt. The purity of the sample was found to be $99.18 \pm 0.26\%$ according to the reported method [2].
2. Terfenadine, working standard, kindly supplied by Misr, Cairo, Egypt. The purity of the sample was found to be $99.73 \pm 0.53\%$ according to the USP (XXIII) 1995 method [16].
3. Flunarizine hydrochloride, working standard, kindly supplied by Glaxo, Cairo, Egypt. The purity of the sample was found to be $99.70 \pm 0.41\%$ according to the reference method [11].

2.2.2. Market samples

1. Hismanal tablets (Glaxo), batch No. 61624 A. Each tablet was labelled to contain: astemizole 10.00 mg, lactose hydrous 27.50 mg, microcrystalline cellulose 18.00 mg, pregelatinized starch 3.60 mg, povidone 1.20 mg, magnesium stearate 0.60 mg, colloidal silicon dioxide 0.40 mg and sodium lauryl sulphate 3.60 mg.
2. Histaminal suspension (Pharco), batch No. 102. Each 1 ml was labeled to contain: astemizole 2.0 mg, sucrose 200.0 mg, alcohol 50.0 mg microcrystalline cellulose and sodium carboxymethyl cellulose 12.0 mg, sodium phosphate 4.245 mg, polysorbate 20.20 mg, sodium chloride 1.00 mg, raspberry 0.7238 mg red current 0.721 mg, sodium biphosphate 0.450 mg and purified water QS 1.00 mg.
3. Terfine tablets (Misr), batch No. R3. Each tablet was labeled to contain terfenadine 120.0 mg, maize starch 70.0 mg, sodium citrate 50.0 mg, ludipress 200.0 mg, sodium starch glycolate 15.0 mg, magnesium stearate 9.0 mg and hydroxy propyl methyl cellulose 5.0 mg.
4. Sibelium capsules (Glaxo), batch No. 50405 B. Each capsule was labeled to contain flunarizine hydrochloride 5.9 mg, lactose 122.7 mg, maize starch 20.0 mg, talc 9.0 mg, magnesium stearate 2.0 mg and colloidal silicon dioxide 0.4 mg.

2.2.3. Reagents

All chemicals used are of analytical grade and are used without further purification.

1. Eosin (Sigma), 2.0×10^{-3} M, aqueous solution, stable for 2 weeks.
2. Lead acetate (Merck), 2.0×10^{-3} M, aqueous solution, stable for 2 weeks.
3. Methylcellulose (MC) (1500 CPS, Aldrich), 0.5% in cold water, stable for two weeks.
4. Buffer solution pH 4.5, prepared by mixing 0.2 M acetic acid and 0.2 M sodium acetate solution, needed to be checked periodically.
5. Deionized water.
6. Astemizole, stock standard solutions (1.0×10^{-3} M), freshly prepared by dissolving in 2 ml 0.2 M acetic acid and complete to volume with water.
7. Terfenadine stock standard solutions (1.0×10^{-3} M), freshly prepared by dissolving in 2 ml 0.2 M acetic acid, warm if necessary and complete to volume with water.
8. Flunarizine hydrochloride stock standard solutions (1.0×10^{-3} M), aqueous solution, freshly prepared.

2.3. Procedure

2.3.1. Spectrophotometric assays

2.3.1.1. Calibration curves. About 23 mg of each drug were accurately weighed and transferred into a 50 ml volumetric flask. The powder was dissolved in 2 ml 0.2 M acetic acid in case of (I) and (II) and water for (III). The volume was completed to the mark with water.

An aliquot of each drug stock solution equivalent to 14.7–114.7, 11.8–47.2 and 2.4–19.1 μg ml^{-1} of (I), (II) and (III), respectively, was transferred to a 10 ml volumetric flask. A 1 ml aliquot of a 0.5% MC solution was added to each of (I) and (II) and 1.5 ml to (III); then 3 ml of the buffer solution (pH 4.5) were transferred to each solution. A total of 1.5 ml each of eosin and lead(II) solutions was added to (I) and 0.75 ml was added to each of (II) and (III). Each mixture was diluted to 10 ml with water, kept at 60°C for 20 min and then cooled for 5 min under tap water. The absorbance was measured at 547.5 nm for (I) and (III) and at 540.7 nm for (II) against a reagent blank.

2.3.1.2. Assay of drugs in pharmaceutical formulations

2.3.1.2.1. Tablets. Ten tablets of each of astemizole and terfenadine were accurately weighed and ground into a fine powder. A weight of powder equivalent to (1.0×10^{-3} M) of the drug was transferred to 50 ml volumetric flask, dissolved in 2 ml 0.2 M acetic acid, completed to volume with water and filtered. The procedure was completed as under Section 2.3.1.1

2.3.1.2.2. Suspensions. The bottle was shaken well before use. An aliquot volume of suspension equivalent to (1.0×10^{-3} M) of the active constituent was transferred into a 50 ml volumetric flask and completed to volume with 0.2 M acetic acid. The flask was shaken well and filtered. The assay was completed as under Section 2.3.1.1.

2.3.1.2.3. Capsules. The contents of twenty capsules were emptied and a known weight of the powder equivalent to (1.0×10^{-3} M) of the drug was transferred into a 50 ml volumetric flask dissolved in water, completed to volume and filtered. The assay was completed as under Section 2.3.1.1.

2.3.2. Fluorometric assays

2.3.2.1. Calibration curves. A sample solution containing up to 0.94–7.1 μg ml^{-1} (15×10^{-6} M) of each drug was transferred into a 10 ml volumetric flask. To this solution, 1 ml MC solution for (I) and (II) and 1.5 ml for (III), 3 ml buffer solution pH 4.5, 0.4 ml of eosin (2.0×10^{-5} M) and 0.4 ml of Pb(II) (2.0×10^{-5} g) solution were added subsequently. The mixture was diluted to volume with water, kept at 60°C. for 20 min and then cooled for 5 min under tap water. The difference of the relative fluorescence intensity was measured at 545 nm emission with excitation at 462 nm against a reagent blank.

2.3.2.2. Assay of drugs in pharmaceutical formulations

2.3.2.2.1. Tablets. Ten tablets of estemizole and terfenadine were accurately weighed and ground

into a fine powder. A weight of powder equivalent to (1.0×10^{-3} M), of the drug was transferred into a 50 ml volumetric flask, dissolved in 2 ml 0.2 M acetic acid, completed to volume with water and filtered. An aliquot of each drug equivalent to 0.94–7.1 μg ml^{-1} was transferred into a 10 ml volumetric flask and completed as under Section 2.3.1.1.

2.3.2.2.2. Suspensions. The bottle was shaken well before use. An aliquot volume of suspension equivalent to (1.0×10^{-3} M) of the drug was transferred into a 50 ml volumetric flask and completed to volume with 0.2 M acetic acid. The flask was shaken well and filtered. The assay was completed as under Section 2.3.2.2.1.

2.3.2.2.3. Capsules. The contents of twenty capsules were emptied and a known mass of the powder equivalent to (1×10^{-3} M) of the drug, was transferred into a 50 ml volumetric flask, dissolved in water, completed to volume and filtered. The assay was completed as under Section 2.3.2.2.1.

3. Results and discussion

The main purpose of this study was to establish simple spectrophotometric and fluorometric methods for the determination of some antrihistaminics in their pharmaceutical dosage forms without prior extraction. Two proposed methods using ternary complex formation with eosin and lead(II) are described.

Ternary complexes formed between the metal ion: electronegative ligand and organic base often have higher values of molar extinction coefficient than ordinary (double) complexes of the same components. The formation of ternary complexes were reported to improve not only the sensitivity but also the selectivity as well. A typical feature is that in ternary complexes the third component does not weaken the bond between the first two, but sometimes even reinforces the stability of the complex [17].

Ternary complex formation had been used for determination of Pd(II) via 1,10 phenanthroline as a cationic component and eosin as an anionic counter ion [18]. On the same basis, Fujita et al. [19] determined a group of drugs by formation of ternary complex with Pd(II) and eosin. In their studies nine cations had been tried; Pd(II) was proved to be the only effective metal ion.

In the present study, trials to use Pd(II) as complexing ion with the studied drugs were unsatisfactory. Among the studied metal ions, Pb(II) gave the highest sensitivity and reproducibility. It was therefore used in this study. Appropriate conditions were established for the colour reaction and for the eosin: Pb(II): drug ratio to reach maximum sensitivity.

3.1. Spectrophotometric assays

Colour reactions of various drugs in aqueous media was investigated by utilizing the ternary complex formation between the studied drug–metal ion [Pb(II) $(drug)_n$] as cation and (eosin) as anion. This ion-pair association complex has the selective and specific nature of the cation complex for each drug.

Optimum conditions for the reactions were established for the spectrophotometric determination of (I), (II) and (III) by using eosin and Pb(II).

When the effect of pH on complex formation was studied, it was found that the optimum pH is in the range of 3.8–4.5, using acetate buffer; 3 ml of the buffer solution were adequate to obtain the maximum and constant absorbance when measuring the test solution against the reagent blank, for the three studied drugs.

When a non ionic surfactant methylcellulose (MC) was used, prior extraction steps were unnecessary. The addition of surfactants to solubilize and stabilize the ternary complex had been previously reported [19]. Cationic surfactants such as cetylpyridinium chloride depressed the coloured complex formation probably due to the formation of an ion-pair complex between eosin and the cationic surfactant. MC, which is a non ionic water-soluble polymeric surfactant, was reported to be the best dispersing agent with respect to sensitivity [19]. Accordingly, MC was used.

In this study, addition of MC was also found to be necessary for complex stability and prevention of precipitate formation.

The acid dissociation properties of eosin in the presence of MC were determined spectrophotometrically at an ionic strength of 0.1 at 20 ± 0.1°C [20,21]. Depending on the pH of the solution, eosin can exist in any of the following forms:

$$H_3R^* \overset{K_{a_1}}{\rightleftharpoons} H_2R \overset{K_{a_2}}{\rightleftharpoons} HR^- \overset{K_{a_3}}{\rightleftharpoons} R^{2-}$$

where R denotes the undissociated parts of eosin. In this study, the pK_{a1}, pK_{a2} and pK_{a3} in the presence of MC were 2.10, 2.85 and 4.95, respectively. At pH 4.3 about 80% of eosin was found to be in the form HR [22].

The effect of eosin and Pb(II) concentrations was examined by varying the molar ratio of eosin to Pb(II), while keeping the Pb(II): drug ratio constant. Maximum absorbance was observed when the molar ratio of Pb(II) to eosin was approximately 1:1 taking into consideration the determination of drug limits. This shows the importance of the concentrations of Pb(II) and eosin. The composition of the ternary complexes obtained by the molar ratio method, the molar absorptivity (ϵ), and the relative standard deviations (R.S.D., $n = 5$) are shown in Table 1.

The effects of temperature and time were also studied. The colour development at room temperature was very slow, more than 24 h being required. Maximum absorbance was obtained at 60°C, after 20 min. The solution was cooled under tap water to room temperature with agitation before measuring the absorbance to solubilize jelly-like aggregates formed upon heating at 60°C. As reported by other investigators, the reproducibility was somewhat poor on using hot solution [23].

Under the above described conditions, (I) and (III) were measured at 547.5 nm while (II) was measured at 540.7 nm.

3.2. Fluorometric assays

It was envisaged that due to ternary complex formation reduction of fluorescence may occur. Thus, a fluorescence quenching method for the determination of (I), (II) and (III) was also investigated. The relative emission spectra of test and blank solutions are shown in Fig. 1. On the addition of the drug to the solution mixture, the relative fluorescence intensity (R.F.L. int) decreased significantly compared with blank; the magnitude of the decrease was proportional to the concentration of the drug.

In the development of the recommended procedure for the fluorometric assay of the drugs, the amounts of eosin and Pb(II) were varied, keeping the same conditions as for spectrophotometric assays. The optimum amount of each of eosin and Pb(II) was 0.4 ml of 2×10^{-5} in the final volume of 10 ml.

3.3. Calibration

Calibration curves construction for the spectrophotometric method gave linear relationship for astemizole(I), terfenadine(II) and flunarizine hydrochloride(III) in the concentration ranges 4.1–37.6 μg ml^{-1} of (I), 11.8–47.2 μg ml^{-1} of (II) and 2.4–19.1 μg ml^{-1} of (III) with the following regression equations:

$A = 0.003 + 0.03C \qquad r = 0.9989 \quad$ for (I)

$A = 0.005 + 0.019C \qquad r = 0.9997 \quad$ for (II)

$A = 0.005 + 0.065C \qquad r = 0.9999 \quad$ for (III)

where A is the absorbance, C is concentration in μg ml^{-1} and r is correlation coefficient.

Table 1
Molar absorptivity, relative standard diviation and complex composition of studied drugs obtained by the proposed spectrophotometric method

Drug	ϵ	R.S.D.* (%)	Molar ratio Pb:eosin:drug
Astemizole	14.93×10^3	0.64	3:3:1
Terfenadine	92.33×10^2	0.39	3:3:1
Flunarizine hydrochloride	321.67×10^3	0.47	2:2:1

* Relative standard deviation ($n = 5$).

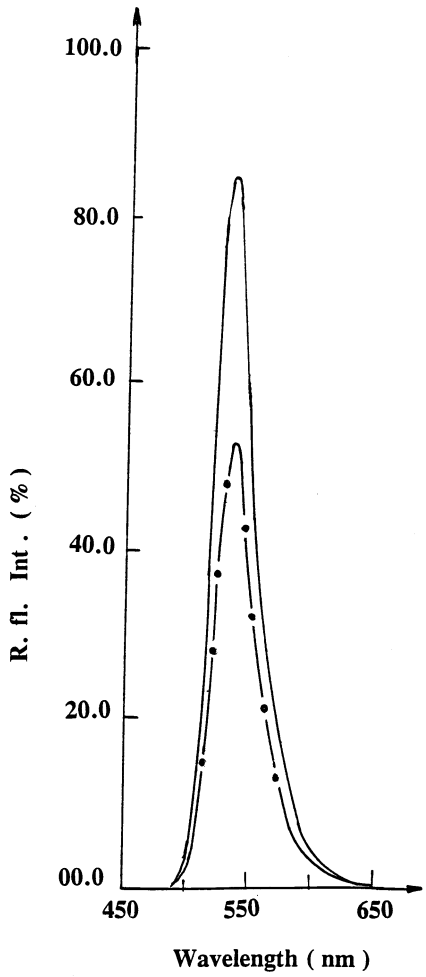

Fig. 1. Quenching effect of complex formation on Eosin–Pb(II) emission spectra Eosin–Pb(II), Flunarizine Hydrochloride (5 μg ml^{-1})—Eosin–Pb(II).

The concentration range for the fluorometric assay was 0.94–7.1 μg ml^{-1} for (I), (II) and (III). The data fit the regression equations for straight line as follows:

$\Delta I_F = 0.6 + 11.64C \quad r = 0.9996$ for (I)

$\Delta I_F = 1.29 + 12.06C \quad r = 1.001$ for (II)

$\Delta I_F = 1.45 + 12.66C \quad r = 0.9997$ for (III)

Where ΔI_F is the quenching in the relative fluorescence intensity, C is concentration in μg ml^{-1} and r is correlation coefficient.

3.4. Precision

The suggested methods were successfully applied to the determination of the studied drugs in both raw material and pharmaceutical dosage forms. The precision was calculated by performing five analyses of each sample. The relative standard deviation (R.S.D.) was determined and the results obtained were compared statistically with those obtained by applying the official or reported methods (Tables 2 and 3).

3.5. Validation

The validity of the proposed methods was assessed by applying the standard addition technique. The results obtained are presented in Table 3.

Tables 2 and 3 show that the calculated t and F values are less than the corresponding theoretical values indicating that there is no significant difference between the two methods and the reference or official method with respect to both precision and accuracy. Also this indicate a good reproducibility and repeatability.

4. Conclusion

Colour reaction among various drugs, eosin and Pb(II) were examined. Spectrophotometric and fluorometric methods for astemizole (I), terfenadine (II) and flunitanne hydrochloride (III) were accordingly established by using ternary complex formation. The ternary complex formed in this reaction system was regarded as the ion-association complex between (Pb(II) $(drug)_n$) cation and eosin anion. Compared with the conventional methods using organic dyes or metal ion alone, the present methods do not require prior extraction procedure and have the advantages of simplicity, sensitivity and reproducibility. The present procedure is useful and convenient for quality control and routine determination of drugs in pharmaceutical dosage forms where precision, time and cost effectiveness of analytical methods are important.

Table 2
Statistical comparison between the determination of astemizole, terfenadine and flunarizine hydrochloride by the proposed methods and the official or reference methods

	Astemizole			Terfenadine			Flunarizine hydrochloride		
	Spectrophotometric method	Fluorophotometric method	Reference method [2]	Spectrophotmtric method	Fluorophotometric method	Official method [16]	Spectrophotometric method	Fluorophotometric method	Reference method [11]
Mean* ± R.S.D.%	99.20 ± 0.63	99.84 ± 0.29	99.18 ± 0.26	99.76 ± 0.39	99.24 ± 0.36	99.73 ± 0.53	99.60 ± 0.47	99.34 ± 0.26	99.70 ± 0.41
Concentration range	4.1–37.6 μg ml^{-1}	0.94–7.1 μg ml^{-1}	5–30 μg ml^{-1}	11.8–47.2 μg ml^{-1}	0.94–7.1 μg ml^{-1}	50–200 mg	2.4–19.1 μg ml^{-1}	0.94–7.1 μg ml^{-1}	4–20 μg ml^{-1}
C.V.	0.64	0.29	0.26	0.39	0.36	0.53	0.47	0.26	0.41
Correlation coefficient	0.9989	0.9996		0.9997	1.001		0.9999	0.9997	
Variance	0.409	0.082	0.068	0.152	0.130	0.281	0.221	0.07	0.169
N	5	5	5	5	5	5	5	5	5
F	2.42 (6.4)	4.99 (6.4)		1.39 (6.4)	1.29 (6.4)		1.15 (6.4)	2.4 (6.4)	
t	1.66 (2.31)	2.13 (2.31)		0.10 (2.31)	1.36 (2.31)		0.35 (2.31)	1.7 (2.31)	

* The average of five experiments.

Table 3
Determination of astemizole, terfenadine and flunirazine hydrochloride in pharmaceutical formulations using the proposed methods and official or reference methods

Preparation	% Recovery[a]		
	Spectrophotometric method	Fluorophotometric method	Reference method
Astemizole			
Hismanal tablets [2]	99.60 ± 0.38	99.8 ± 0.25	99.72 ± 0.22
10 mg tablet^{-1}	$F = 3$ (6.4)	$F = 1.30$ (6.4)	
B.N. 61624 A	$t = 0.62$ (2.31)	$t = 1.35$ (2.31)	
Histaminal suspension [2]			
1 mg ml^{-1} suspension	99.72 ± 0.41	99.64 ± 0.52	100.02 ± 0.27
B.N. 102	$F = 2.30$ (6.4)	$F = 3.70$ (6.4)	
	$t = 1.37$ (2.31)	$t = 1.46$ (2.31)	
Terfenadine			
Terfine tablets [16]	99.56 ± 0.31	99.78 ± 0.24	99.80 ± 0.56
120 mg tablet^{-1}	$F = 3.26$ (6.4)	$F = 5.45$ (6.4)	
B.N. R3	$t = 0.83$ (2.31)	$t = 0.07$ (2.31)	
Flunarizine hydrochloide			
Sibelium capsules [11]	99.98 ± 0.15	100.01 ± 0.13	100.00 ± 0.14
5 mg capsule^{-1}	$F = 1.15$ (6.4)	$F = 1.15$ (6.4)	
B.N. 50465 B	$t = 2.22$ (2.31)	$t = 0.12$ (2.31)	

Theoretical value: $t = 2.31$ at the 95% confidence level.
Theoretical value: $F = 6.4$ at the 95% confidence level.
[a] The average of five determinations $\pm$ standard deviation.

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