ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Spectrophotometric Determination of Clemastine hydrogen fumarate, Fexofenadine HCl and Moxepril HCl through Ion-Pair Formation with Chromatrope 2 R.

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ABSTRACT

Simple, accurate spectrophotometric methods have been estimated for the microdetermination of clemastine hydrogen fumarate (I), fexofenadine HCl (II) and moxepril HCl (III). The proposed method is based on the formation of ion-pair complexes between the examined drugs with chromatrope 2 R.The coloured products had absorption maxima at 510 nm for (I) ,512 nm for (II) and (III). Appropriate conditions were established for the colour reaction between chromatrope 2 R and the studied drugs to obtain maximum sensitivity. Under the proposed conditions, the method is applicable over concentration range of (10-60), (30-120) and (20-200) for (I), (II) and (III) respectively. The molar absorptivity (ε), sandell sensitivity, detection (LOD) and quantitation limits (LOQ) are calculated. The procedure was favorably applied for the determination of certain pharmaceutical dosage forms containing the studied drugs. The obtained results demonstrated that the method is equally accurate, precise & reproducible as the official or reported methods.

Keywords: Clemastine hydrogen fumarate, Fexofenadine HCl, Moxepril HCl, Chromatrope 2 R, Binary complex.

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ISSN: 0975-8585

INTRODUCTION

Clemastine (I) used as the hydrogen fumarate in hay fever, rhinitis, allergic skin conditions, and pruritus. It causes drowsiness, few procedures are described for the determination of CMT including spectrophotometry [1–4], HPLC [5–7], gas chromatography [8, 9].

Fexofenadine HCl (II) is a potent long-acting histamine H_1-receptor antagonist. Few analytical methods have been reported for its determination including spectrophotometric methods [10-16] and high performance liquid chromatography (HPLC) [10, 17-22].

Moexipril hydrochloride (III) is a new potent orally active non-sulfhydryl angiotensin-converting enzyme (ACE) inhibitor which is used for the treatment of hypertension and congestive heart failure. A few analytical methods have been developed for the determination of moexipril, including derivative spectrophotometric [23], spectrophotometric methods [24]. RP-HPLC methods have been developed for the simultaneous determination of moexipril [23, 25 and 26]. A gas chromatographic-mass spectrometric method [27] has been developed for moexipril and its active metabolite oexiprilate in human plasma

Chromatrope 2R , is 3-(phenylazo) chromotropic acid, disodium salt. Chromotropic acid is used for preparation of azo dyes which are well known indicators for spectrophotometric determination of metal ions [28,29]. Some chromotropic acid azo dyes have been used for extraction spectrophotometric determination of sildenafil citrate [30], pipazethate hydrochloride [31], neomycine sulphate [32], meclozine hydrochloride [33].

The present work aims to present a simple, rapid and sensitive method for the determination of clemastine hydrogen fumarate, fexofenadine HCl, moxepril HCl, in pure form and in their pharmaceutical preparations and can be used for the quality control and assurance of these drugs in industry. The method is based on the formation of ion-associate between the cited drugs and chromatrope 2 R.

EXPERIMENTAL

Apparatus

A shimadzu recording spectrophotometer UV 1201 equipped with 10 mm matched quartz cells.

Materials and reagents

Chemicals of analytical grade and double distilled water were used throughout the work. Clemastine hydrogen fumarate, Tavegyl® tablets labelled to contain1 mg clemastine per tablet and Tavegyl® ampoules labelled to contain 2 mg clemastine per 2 mL (Novartis Company for Pharmaceuticals, Egypt). Fexofenadine HCl, Rapido® capsules contain 120 mg fexofenadine HCl per capsule (Sedico Company for Pharmaceuticals, Egypt) and telfast®

tablets contain 120 mg fexofenadine HCl per tablet (Aventis Company for Pharmaceuticals, Egypt).
Moexipril hydrochloride, Primox® tablets labelled to contain 15 mg moexipril hydrochloride per tablet (Minapharm Company for pharmaceuticals, Egypt). chromatrope 2R was obtained from Aldrich (USA), (5×10^{-3} M), was prepared
by dissolving 0.2341 g in 100 ml distilled water.

Standard solutions

Preparation of clemastine hydrogen fumarate and Fexofenadine HCl standard solutions

Stock working solutions was prepared to contain 1 mg/ml, dissolved in least amount of methanol (3 ml) then the volume was completed with double distilled water.

Preparation of moxepril HCl standard solutions

Stock working solution was prepared to contain 1 mg/ml, dissolved in distilled water and completed to the mark with the same solvent.

General procedure

Different aliquots of standard solutions [equivalent to (0.1-0.6), (0.3-1.2), (0.2-2)mg of (I), (II) and (III) were transferred into series of 60 ml separating funnels, followed by specific volumes of different acids of certain molarities then specified amounts of chromatrope 2 R were added for the studied drugs (Table 1). The formed ion pairs were extracted with 10 ml methylene chloride. The solutions were vigorously shaked and the separated organic layer dried over anhydrous sodium sulphate and transferred into 10 ml volumetric flasks. The absorbances of the colored solutions were measured at 510 nm for (I), 512 nm for (II) and (III) against reagent blank treated similarly. All measurements were made at ambient temperature.

Procedure for pharmaceutical formulations

For tablets and capsules

A accurately weighted quantity of the well mixed powders were dissolved in distilled water except for (I) and (II) were extracted with methanol(3ml), then the volumes were completed to the mark with distilled water in 25 ml calibrated flasks, filtered and the assay was completed as under general procedure.

For Tavegyl ampoule

Accurate volume of tavegyl vial equivalent to 25 mg of clemastine hydrogen fumarate was measured, completed to 25 ml with double distilled water and the procedure was completed as under general procedure.

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Stoichiometric relationship

Job's method of continuous variations [34] was employed using equimolar (5×10^{-4}, 5×10^{-3} and 2.5×10^{-3}M) standard solutions of clemastine hydrogen fumarate, Fexofenadine HCl and moxepril HCl with chromatrope 2 R (5×10^{-4}, 5×10^{-3} and 2.5×10^{-3}M) respectively.

A series of solutions were prepared in which the total volume of drugs and chromatrope 2 R was kept at 6.0 mL for clemastine hydrogen fumarate, Fexofenadine HCl while kept at 3 ml for moxepril HCl then complete the procedure as under the above mentioned procedure.

RESULTS AND DISCUSSION

The studied drugs reacted with chromatrope 2 R through an ion-pair salt formation, forming a reddish orange chromophore with λmax at 510 nm for (I), while was measured at 512 nm for (II) and (III) (Fig. 1).

Several parameters such as acidity, type and amount of acid added, reagent volume, sequence of addition and effect of extracting solvent were optimized to achieve high sensitivity, stability, low blank reading and reproducible results.

Effect of acidity

In a trial to elucidate the optimum medium for the quantitative determination of the studied drugs the effect of sulphuric, acetic and hydrochloric acids was examined. The highest absorbance values and high stability were obtained in the presence of 0.2, 3 ml of 1, 2 M acetic acid for (I), (II) respectively or 0.7 ml 4.5 M H_2SO_4 in case of (III). (Fig 2)

Effect of the reagent volume

The effect of reagent volume was tested by using varying amounts (0.5–3) ml of 5×10−3 M solution of chromatrope 2 R The results showed that 1 ml of 5×10−3 M of C2R was sufficient for the production of maximum and reproducible colour intensity for all the studied drugs (Fig.3).

Effect of sequence of mixing

The most favourable sequence was drug–acid-reagent for the production of the highest colour intensity, while the other sequences produce lower absorbance values.

Effect of time and temperature

The effect of time on the formation and stability of the ion-associates was studied by measuring the absorbances of the extracted ion-associates at increasing time intervals. The results showed that the ion-associates were formed almost after 5 min in all cases at room

temperature (25±5 °C). In the case of clemastine hydrogen fumarate, Fexofenadine HCl the developed colour remained stable for 3-4 hrs and more than one week when kept in refrigerator for clemastine. In the case of moxepril HCl, the developed colour remained stable for 40 min. After these intervals, a slight decrease in colour intensity occurred. (Fig 4).

Effect of extracting solvent

The polarity of the solvents affects extraction, efficiency and absorptivity of the ion associates. Several water–immiscible organic solvents including toluene, chloroform, methylene chloride and ethylene chloride were tried. The most convenient solvent found to produce the highest absorbance, extraction power and stability of colour of the formed ion-associates was methylene chloride.

The stoichiometric ratio of the ion-associate

The stoichiometry of the ion-associates formed between the drugs under investigation and the reagents was investigated by applying the continuous variation [34] method at the wavelengths of maximum absorbance. The results obtained showed that the stoichiometric ratio of the ion-associates is 1:2 (reagent:drug) in all cases.(Fig 5)

Method validation

Under the described experimental conditions, standard calibration curves for, clemastine hydrogen fumarate , fexofenadine HCl and moxepril HCl with chromatrope 2 R were constructed by plotting absorbance against concentration. Conformity with Beer's law was evident in the concentration range of the final dilution cited in (Table 1). The linear regression equation for each drug was listed in (Table 1). The correlation coefficient was 0.9998 0.9999 indicating good linearity.

Analytical applications

The proposed method was applied to determine the studied drugs in their pharmaceutical dosage forms. Satisfactory results were obtained. To check the validity of the proposed method, the standard addition technique was applied by adding them to the analyzed pharmaceutical dosage forms. The recovery of each drug was calculated by comparing the concentration obtained from the spiked mixtures with those of the drug. The results of analysis of the commercial dosage forms and the recovery study as shown in (Tables 2, 3). The results obtained were compared with the official and reported methods [16, 23 and 35]. No significant differences were found between the proposed methods and official or reported methods. Statistical comparison of the results was performed using student-t-test and F-ratio at 95% confidence level. (Table 4).

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Parameter	*Clemastine hydrogen fumarate*	Fexofenadine HCl	*Moexipril HCl*
λ max (nm)	510	512	512
Beers law limits (µg/ml)	10-60	30-120	20-200
Type and molarity of acid	1 M HAC	2 M HAC	4.5 M H_2SO_4
Volume of acid	0.2 ml	3ml	0.7ml
Chromatrope 2R volume	1 ml	1 ml	1 ml
Reaction time (min)	5	5	5
Extracting solvent	methylene chloride	methylene chloride	methylene chloride
Regression equation**			
Slope (b)	0.02	0.0095	0.0036
Intercept (a)	-0.1589	-0.1459	0.0572
Correlation coefficient (r^2)	0.9999	0.9999	0.9998
LOD µg/ml	0.65	0.45	0.96
LOQ µg/ml	2.17	1.5	3.2
Sandell sensitivity µg.cm^{-2}	0.08	0.14	0.23
ε ($\times 10^4$) L.mol^{-1}.cm^{-1}	0.45	0.37	0.23

Table 1: Characteristic parameters for the reaction of studied drugs with Chromatrope 2R*.

*Average of three experiments
** A=a + bc

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Table 2: Application of the standard addition technique to the spectrophotometric determination of the studied drugs I-II with Chromatrope 2R in pharmaceutical dosage forms*.

Tavegyl® tablets				*Tavegyl ® ampoules*				*Telfast® tablets*			
Claimed taken Mg/ml	Authentic added µg/ml	Found conc. µg/ml	Recovery %	Claimed taken µg/ml	Authentic added µg/ml	Found conc. µg/ml	Recovery %	Claimed taken µg/ml	Authentic added µg/ml	Found conc. µg/ml	Recovery %
15		14.82	98.79	15		14.82	98.79	30		30.20	100.67
	10	10.20	101.96		10	10.10	100.95		20	20.31	101.53
	15	15.17	101.14		15	14.92	99.46		30	29.99	99.96
	20	19.94	99.72		25	24.82	99.28		40	40.31	100.76
	25	24.82	99.28		30	30.35	101.16		60	59.78	99.63
	30	29.84	99.48		35	35.32	100.92		70	70.83	101.19
	35	35.42	101.21		40	39.74	99.36		80	81.15	101.43
	40	40.35	100.87		45	45.77	101.72		90	90.41	100.46
	50	50.40	100.79		50	50.40	100.79				
Mean			100.56				100.46				100.71
Variance			0.91				0.89				0.53
S.D.			0.95				0.94				0.73
S.E.			0.34				0.33				0.28

* Average of three experiments

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Rapido® capsules				*Primox® tablets*			
Claimed taken Mg/ml	**Authentic added µg/ml**	**Found conc. µg/ml**	**Recovery %**	**Claimed taken µg/ml**	**Authentic added µg/ml**	**Found conc. µg/ml**	**Recovery %**
30		30.31	101.02	40		40.36	100.90
	20	20.09	100.47		20	19.81	99.03
	30	29.99	99.96		40	40.36	100.90
	40	40.41	101.03		60	60.08	100.14
	50	50.94	101.87		80	79.53	99.41
	60	60.41	100.68		100	100.92	100.92
	70	70.94	101.34		140	141.19	100.85
	80	79.36	99.20		160	158.69	99.18
	90	90.09	100.11				
Mean			100.58				100.06
Variance			0.71				0.72
S.D.			0.84				0.85
S.E.			0.30				0.32

Table 3: Application of the standard addition technique to the spectrophotometric determination of the studied drugs (II-III) with chromatrope 2 R in pharmaceutical dosage forms*. * Average of three experiments

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Table (4): **Determination of clemastine hydrogen fumarate , fexofenadine HCl and moxepril HCl by chromatrope 2 R method compared with official or reported methods.**

Drug	***chromatrope 2 R method***		***Official or reported methods***
Clemastine hydrogen fumarate	*Mean ±R.S.D*	99.84 ± 0.653	99.74 ±0.452 [35]
	Variance	0.43	0.2
	Student-t-test	0.24(1.81)*	--
	f-test	2.09 (4.46)*	--
	n	9	3
Fexofenadine HCl	***Mean ±R.S.D***	100.21 ± 0.422	100 ± 0.85 [16]
	Variance	0.18	0.72
	Student-t-test	0.6 (1.79)*	--
	f-test	4 (4.12)*	--
	n	8	5
Moxepril HCl	***Mean ±R.S.D***	100.48 ± 0.762	99.86±0.66 [23]
	Variance	0.59	0.44
	Student-t-test	1.71 (1.74)*	--
	f-test	1.36 (3.48)*	--
	n	6	10

*The figures in parenthesis are the theoretical values for t- and f-tests ($p < 0.05$).

ISSN: 0975-8585

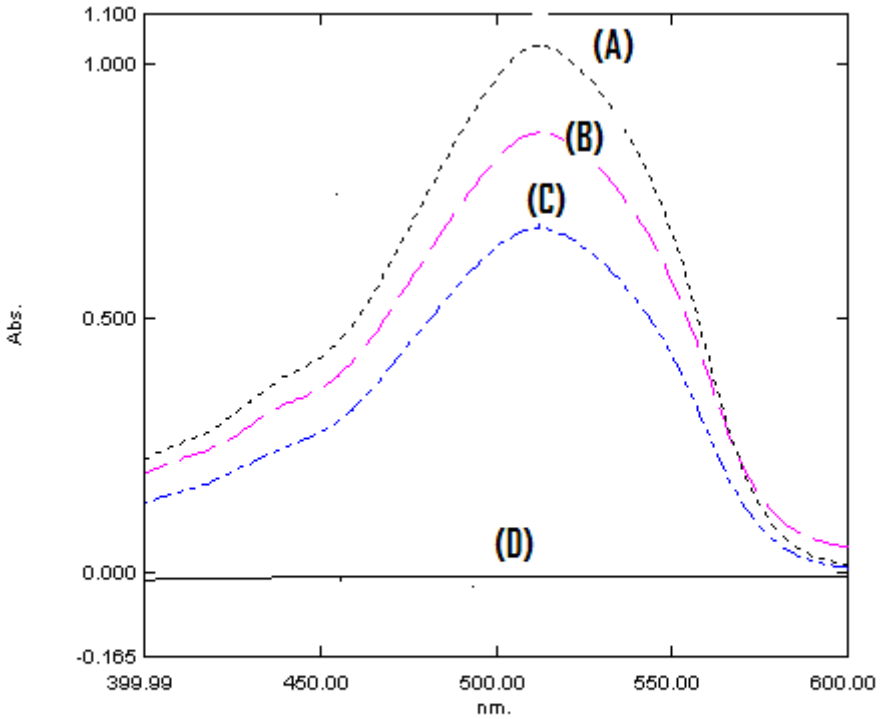

Fig.1: Absorption spectra of the ion pair complex formed between chromatrope 2R and 60 µg/ml clemastine hydrogen fumarate (A), 200 µg/ml moxepril HCl (B) and 100 µg/ml Fexofenadine HCl (C) against blank(D).

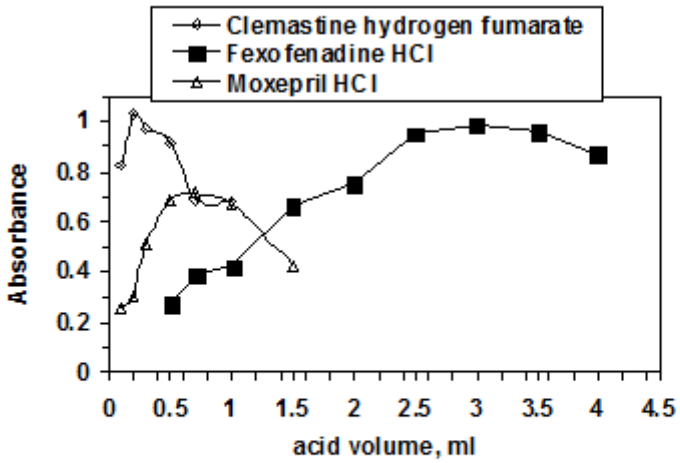

Fig.2: Effect of acid volume on the ion pair complex formation between chromatrope 2R and 60 µg/ml clemastine hydrogen fumarate, 120 µg/ml Fexofenadine HCl, 180 µg/ml moxepril HCl.

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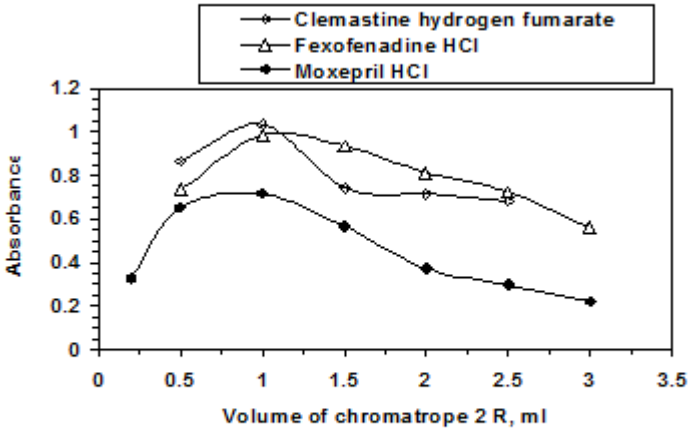

Fig.3. Effect of chromatrope 2R volume on absorbance of 60 µg/ml clemastine hydrogen fumarate, 120 µg/ml Fexofenadine HCl, 180 µg/ml moxepril HCl.

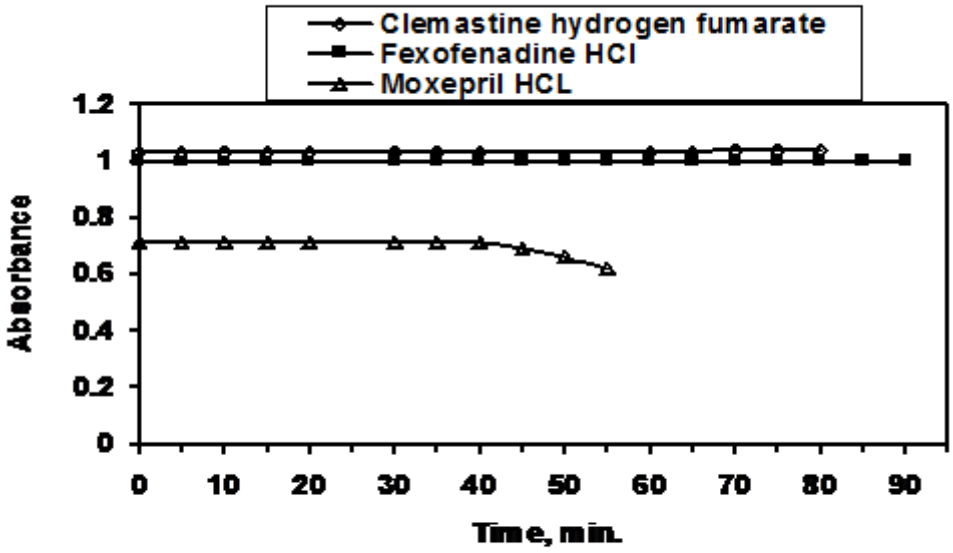

Fig 4: Stability of the ion pair complex formed between chromatrope 2R and 60 µg/ml clemastine hydrogen fumarate, 120 µg/ml Fexofenadine HCl, 180 µg/ml moxepril HCl.

ISSN: 0975-8585

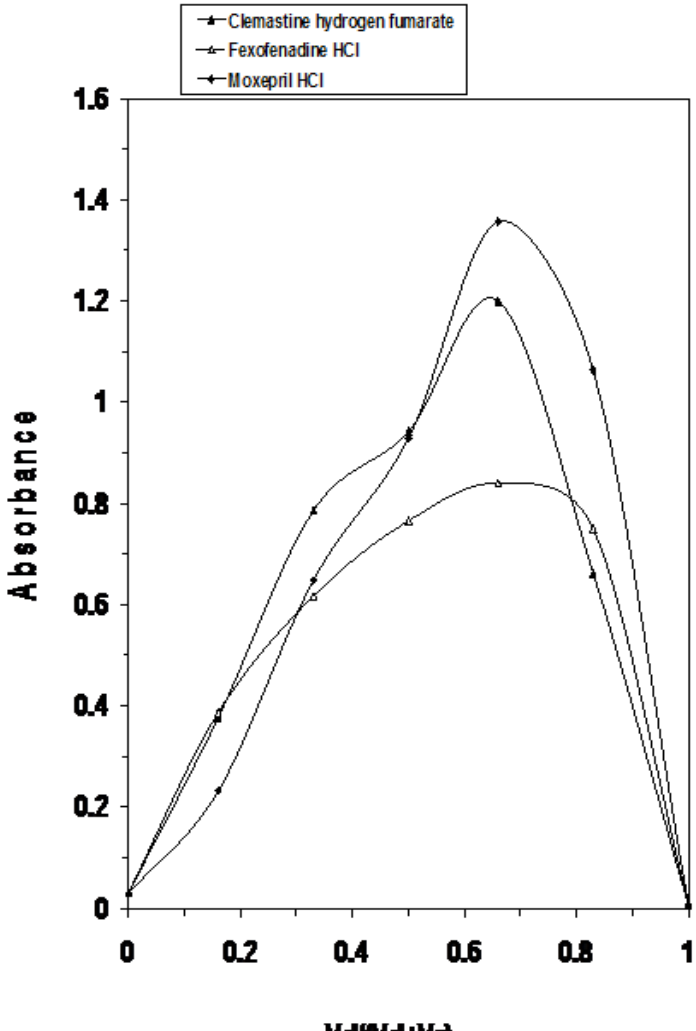

Fig.5: Continuous variation plot for (5×10^{-4}, 5×10^{-3} and 2.5×10^{-3}M) standard solutions of clemastine hydrogen fumarate, Fexofenadine HCl and moxepril HCl with chromatrope 2 R (5×10^{-4}, 5×10^{-3} and 2.5×10^{-3}M) respectively.

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