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Research Article

SPECTROPHOTOMETRIC DETERMINATION OF TERBINAFINE HCl, TELMISARTAN AND RAMIPRIL THROUGH REDOX REACTIONS USING CERIC SULPHATE AND CERIC SULPHATE-CHROMATROPE 2R

Afaf Abou-elkheir*, HanaaSaleh, Magda M. El-henawee and Basma El-sayedGhareeb

Analytical Chemistry Department, Faculty of Pharmacy, Zagazig University, Zagazig, Egypt.

ABSTRACT

Direct (A) and indirect (B) spectrophotometric methods are proposed for the assay of Terbinafine HCl, Telmisartan and Ramipril in bulk drugs and in their dosage forms using ceric (IV) sulphate and ceric (IV) sulphate-chromatrope 2R as reagents. Method (A) involves the addition of certain amount of ceric (IV) sulphate to drugs in acid medium, followed by determination of the decrease in absorbance measured at 319 nm using the experiment as a blank.

Method (B) involves the addition of a known excess of ceric (IV) sulphate to drugs in acid medium followed by the determination of unreacted ceric by reacting with a fixed amount of chromatrope 2R then the decrease in color intensity of C2R was measured spectrophotometrically at λmax 507 nm against the reagent blank.

The Beer's law is obeyed in the concentration range of (1-9) µg/ml (A),(1-7) µg/ml (B) of Terbinafine hydrochloride, (1-5) µg/ml(A),(B) of Telmisartan and (10-80) µg/ml (A), (10-60) µg/ml (B) of Ramipril. The validity of these methods have been successfully applied for the determination of the drugs in there pharmaceutical preparations. Good recoveries were obtained and the results were comparable with those obtained by reference method.

Keywords: Terbinafine hydrochloride, Telmisartan, Ramipril, Ceric sulphate and Ceric sulphate.

INTRODUCTION

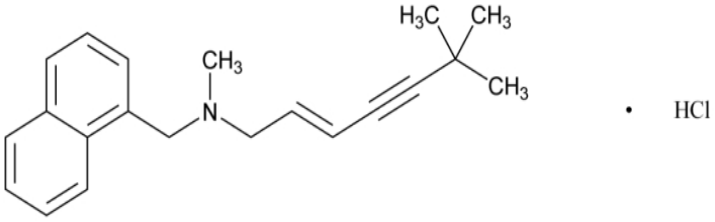
In the present work, spectrophotometric determination of Terbinafine HCl, Telmisartan andRamipril using cerium (IV) and cerium (IV)-chromotrope 2R were described. The proposed methods are simple, accurate and in good agreement with results obtained by reference methods.

Terbinafine Hydrochloride, (TH) chemically is 1-naphthalenemethanamine, n-(6, 6-dimethyl-2-hepten-4-ynyl)-n methyl-, (E)-, hydrochloride (Figure 1). TH is a new potent antifungal agent. It belongs to an allyl amine class and has broad-spectrum activity against yeasts, dimorphic fungi, molds and dermatophytes[1-3].Literature survey shows several HPTLC[4-6], non-aqueous voltametric[7], spectrometric methods[8-12] and ion-pair RP chromatography[13] have been used for assay of TH in raw material and dosage forms. Only stability-indicating HPTLC[12,13] method is reported for determination of the drug. Reported spectrophotometric[9] and chromatographic[14,15] methods estimates TH in presence of its degradant or metabolites. Also TH has been determined in biological fluids (plasma, urine) tissues, nails and cat hair by HPLC[16-18] and in tablets and creams by HPLC[19,20].

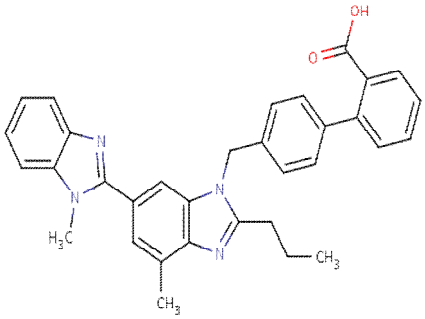
Telmisartan, (TEL)chemically is 4'-[(1, 4'-dimethyl-2'-propyl [2, 6'-bi-1H-benzimidazol]-1'-yl) methyl]-[1, 1'-biphenyl]-2-carboxylic acid (Figure 1). It is indicated in the treatment of essential hypertension. The usually effective dose of Telmisartan is 20, 40 and 80 mg once

daily. Literature survey revealed that there were many methods like Spectrophotometry[21-26] using first order derivative[25]. Simultaneous equation, RP-HPLC[27-30] and LC–MS/MS[31,32] and HPTLC[33,34] for determination of Telmisartan alone and with other drugs in combination have been reported.

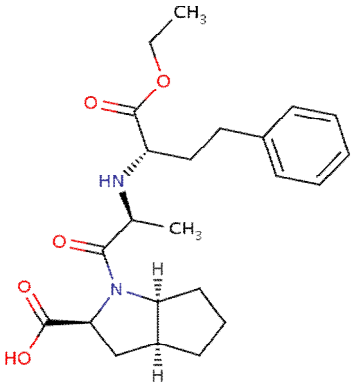
Ramipril, (RP) chemically is [(2S, 3aS, 6aS)-1-[(S)-2- [[(S)-1-(ethoxycarbonyl)-3-phenylpropyl] amino] propanoyl] octa-hydrocyclopenta [b] pyrrole-2-carboxylicacid (Figure 1).RP isan angiotensin-converting enzyme inhibitor(ACEI),which is widely used in the treatment of hypertension and congestive heart failure. RP plays an important role in inhibiting the conversion of the inactive angiotensin I to the active angiotensin II[35-37]. There are many reported methods to determine RP alone or in combination with other in dosage forms and the simultaneous determination of RP in the presence of the degradants[38-40].



Terbinafinehydrochloride



Telmisartan, TEL



Ramipril, RP

Fig. 1: Chemical structure of TH, TEL and RP

Experimental

I. Apparatus

Spectrophotometer: SHIMADZU UV-1800 PC, dual beam UV–visible spectrophotometer with two matched 1 cm quartz cells, connected to an IBM compatible personal computer (PC) and an HP-600 inkjet printer. Bundled UV-PC personal spectroscopy software version (3.7) was used to process the absorption and the derivative spectra. The spectral band width was 0.2 nm with wavelength scanning speed of 2800 nm min−1.

II. MATERIALS AND METHODS

All reagents were of analytical grade and distilled water was used.

1. Terbinafine HCl (Novartis, Egypt).
2. Telmisartan (Boehringer, Egypt).
3. Ramipril (Aventis, Egypt).
4. Cerium(IV) sulphate (Merck, England), 0.15%(TEL, method A), 0.1% (TH, RAM, method A)

, 0.2 % (TH,method B), 0.3 % (TEL, method B), 0.4% (RAM, method B) w/v M solutions by dissolving 0.15, 0.1 ,0.2 ,0.3 0.4gm cerium(IV) sulphate in 0.5,5,1 M sulphuric acid.

5. **Chromotrope 2R**
   2 -(Phenylazo) chromotropic acid disodium salt, (Aldrich, Germany), 0.15 % w/v solution by dissolving 0.15 gmchromotrope 2R in distilled water.

III. Standard drug solutions

1. 0.025gm of Terbinafine HCl and Ramipril dissolved in 25ml distilled water , then further dilution with distilled water to obtain working standard solution of concentration 50µg ml^{-1}.
2. 0.025 gm of Telmisartan dissolved in 25 ml 5M sulphuric acid, then further dilution with 5M sulphuric acid to obtain working standard solution of concentration 100µg ml^{-1}.

IV. Pharmaceutical preparations

1. Lamisil tablets (Novartis, Egypt), labelled to contain 25mg Terbinafine hydrochloride per tablet.
2. Micardis tablets (Boehringer, Egypt), labelled to contain 8 mg Telmisartan per tablet.
3. Tritace protect tablets (Sanofiaventis, Egypt), labeled to contain 10 mg Ramipril per tablet.

V. General procedures

1- Construction of calibration curves

a. Spectrophotometric procedure using ceric(IV) sulphate

To different aliquots of standard solutions containing (1-7), (1-5) and (10-70) µg/ml of Terbinafine HCl, Telmisartan and Ramipril, respectively.For Terbinafine HCl,0.8 ml of 0.1 % w/v cerium(IV) sulphate in 0.5M sulphuric acid solution was added.For Telmisartan, 0.8 ml of 0.15 % w/v cerium(IV) sulphate in 5M sulphuric acid solution was added.For Ramipril, 0.6 ml of 0.1 % w/v cerium(IV) sulphate in 1M sulphuric acid solution was added.The mixtures were heated in a boiling water bath for 36, 30 and 45 min for Terbinafine HCl, Telmisartan and Ramipril, respectively. The test tubes were then cooled and the reaction mixtures were transferred into a series of 10 ml volumetric flasks, the volume was made up to the mark with distilled water. The decrease in absorbance was measured at 319 nm using the experiment as a blank.

b. Spectrophotometric procedure using ceric (IV) sulphate and chromotrope 2R (C2R)

To different aliquots of standard solutions containing (1-7), (1-5) and (10-50) µg/ml of Terbinafine HCl, Telmisartan and Ramipril, respectively. 1ml of 0.2% w/v cerium(IV) sulphate were added for Terbinafine HCl,1ml of 0.3 % w/v cerium(IV) sulphate were added for Telmisartan and 1.2ml of 0.4% w/v cerium(IV) sulphate were added for Ramipril. Mixtures were heated in a boiling water bath for 20, 35 and 35 min for Terbinafine HCl, Telmisartan and Ramipril, respectively, the test tubes were then cooled and the reaction mixtures were then transferred into a series of 10 ml volumetric flasks and 1.4, 1 and 1.6 ml of C2R was added for Terbinafine HCl, Telmisartan and Ramipril, respectively, then the volume was made up to the mark with distilled water. The decrease in color intensity of C2R was measured spectrophotometrically at λmax 507 nm.

2- For pharmaceutical preparations

a. Lamisil tablets

Ten tablets were powdered and an accurately weighed amount equivalent to 10 mg Terbinafine HCl was shaken with distilled water then filtered and diluted to 100 ml with distilled water to obtain working solution of concentration 100µg ml^{-1}.

b. Micardis tablets

Ten tablets were powdered and a weight equivalent to 25 mg of Telmisartan was shaken with cold water for 2 min, to dissolve sorbitol, filtered,washed with 20 ml distilled water and the precipitate was transferred from the filter paper into 25 ml volumetric flask with 5M sulphuric acid then filtered and completed to the mark with 5M sulphuric acid. Further dilution was made to obtain working solution of the concentration 100µg ml-1 using 5M sulphuric acid.

c. Tritace Protect tablets

Ten tablets were powdered and an accurately weighed amount equivalent to 25mg Ramipril was shaken with distilled water then filtered and diluted to 25ml with distilled water,then

further dilution to obtain working solution of concentration 50µg ml^{-1}.
Standard addition technique was used for analysis of the selected drugs in their commercial tablets.

VI. RESULTS AND DISCUSSION

I. Spectrophotometric procedure using ceric sulphate

Cerium (IV) sulphate being a strong oxidizing agent was used for determination of pharmaceutical compounds (41-48). The proposed method based on oxidation of the investigated drugs with excess cerium (IV) sulphate in acidic medium and subsequent measurement of the decrease in reagent absorbance at 319 nm. Figure2,3 and4show absorption spectra of reaction and blank.

Investigation of assay parameters

1. Effect of sulphuric acid concentration

Acid medium is needed to prevent precipitation of the hydrated cerium (IV) oxide (CeO2xH2O). Using different sulphuric acid concentrations ranging from 0.5-5M solutions, the optimum concentration that gave maximum decrease in absorbance were0.5,5,1M solutions for (TH,TEL and RP) respectively.

2. Effect of ceric (IV) sulphate concentration

Maximum decrease in absorbance was obtained using 0.8 ml 0.1% w/v ceric (IV) sulphate, for Terbinafine HCl, 0.8 mL 0.15% w/v ceric (IV) sulphate, for Telmisartan and 0.6 ml 0.1% w/v ceric (IV) sulphate, for Ramipril.

3. Effect of temperature and heating time

Heating for 25 min in a boiling water bath was optimum for Terbinafine HCl, Telmisartan and 45 min in a boiling water bath was optimum for Ramipril.

II. Spectrophotometric procedure using ceric sulphate and chromotrope 2R

The proposed method involves two stages: the first one is the oxidation of the selected drugs with known excess Ce+4 in acidic medium under the effect of heating as explained in the previous paragraph and the second one involves the determination of the unreacted oxidant by measuring the decrease in absorbance of C2R at the suitable λmax 507 nm. Figure 5,6 and 7. The decrease in color intensity is attributed to the oxidation of the dye to its degradable products, results in the formation of formic acid as the main oxidation product.

Investigation of assay parameters

1. Effect of acid type and concentration

The oxidation of Terbinafine HCl, Telmisartan, and Ramipril by cerric sulphate were performed in acid medium. Acid medium is needed to prevent precipitation of the hydrated cerium (IV) oxide (CeO2xH2O). In order to determine the most appropriate acid, different acids (sulphuric, hydrochloric, nitric, perchloric and acetic) were tested, sulphuric acid gave the highest readings.
Using different sulphuric acid concentrations ranging from 0.5-5M solutions, the optimum concentrations that gave maximum decrease in absorbance were 0.5M for Terbinafine HCl, 5M for Telmisartan and 1M for Ramipril.

2. Effect of ceric (IV) sulphate concentration and volume

Maximum increase in absorbance was obtained using 1ml 0.2% w/v ceric (IV) sulphate for Terbinafine HCl, 1ml 0.3% w/v ceric (IV) sulphate for Telmisartan and 1.2 ml 0.4% w/v was the best for Ramipril.

3. Effect of temperature and heating time

Heating for 20min in a boiling water bath was optimum for Terbinafine HCl and 35 min in a boiling water bath was optimum for Telmisartan and Ramipril.

4. Effect of chromotrope 2R (C2R) concentration and volume

Maximum increase in the absorbance was achieved by using 1.4, 1, 1.6ml of 0.15% w/v of C2R for Terbinafine HCl, Telmisartan and Ramipril, respectively.

5. Effect of diluting solvent

The effect of diluting solvent on the absorption intensity of the oxidation reaction of Terbinafine HCl, Telmisartan andRamipril with the different reagents was studied using various solvents for dilution (water, methanol, ethanol, acetontrile, acetone and isopropanol). It was found that water was the optimum diluting solvent for the studied drug as it gave maximum readings Therefore water was selected for further work with all reagents.

VII. Validation of the proposed methods

Linearity

The methods were tested for linearity, accuracy and precision. By using the above procedures, linear regression equations were obtained. The regression plots showed a linear dependence of the absorbance over Beer's law range given in Table 1. The table also shows the results of the statistical analysis of the experimental data,

such as the slopes, the intercepts, the correlation coefficients obtained by the linear least-squares treatment of the results and Molar absorptivity. Results of recovery studies with pure drugs by proposed methods (Table 2) show small values of standard deviation and variance that indicates low scattering of the points around the calibration line and high precision.

Limit of quantitation and limit of detection

The limits of quantitation (LOQ) were determined by establishing the lowest concentration that can bemeasured according to ICH recommendation[49]below which the calibration graph is non linear. The results are shown in Table 1. The limits of detection (LOD) were determined by evaluating the lowest concentration of the analyte that can be readily detected. The results are also summarized in Table 1.

Precision

The precisions of the assays (intra-day and inter-day) were determined for the studied drugs concentrations cited in Table 3. The assays, gave satisfactory results (Table 3). This level of precision of the proposed methods was adequate for the quality control analysis of TER, TEL and RP.

Accuracy

The results obtained were in good agreement with those obtained using the reference methods (50, 51 and 52). Statistical analysis of the result obtained using student t-test and the variance ratio F-test revealed no significance differences between the proposed and references methods regarding the accuracy and precision, respectively (Table 4).

Analytical applications

The results obtained by applying the proposed methods for the determination of drugs in there pharmaceutical formulations (Lamisil, Micardis and Tritace protect tablets) (Table5, 6) suggest satisfactory recovery. Further, standard addition technique followed to check the validity of the method has given good recoveries of the drugs. Hence, these methods can be recommended for adoption in routine analysis of TEL, TER and RP.

VIII. CONCLUSION

The proposed methods are sensitive, enabling accurate and precise determination of TH, TEL and RP over satisfactory concentration ranges without the need for special or laborious sample-pretreatment steps. The methods which are advantageously time and cost-efficient are successfully applied for the quantification of the drugs in commercial samples, with results being in good statistical agreement with reference method. Therefore, the proposed methods are considered useful for routine quality monitoring of pharmaceuticals.

Table 1: Spectral data for determination of Terbinafine HCl, Telmisartan and Ramipril using Cerium (IV) sulphate and cerium (IV) sulphate-chromotrope 2R.A=a + b c**

Parameters	Cerium(IV) sulphate method			Cerium(IV) sulphate + C2R method		
	Terbinafine HCl	Telmisartan	Ramipril	Terbinafine HCl	Telmisartan	Ramipril
Linearity range ($\mu g ml^{-1}$)	1-7	1-5	10-70	1-7	1-5	10-50
Wavelength (nm)	319	319	319	507	507	507
Limit of detection (LOD) ($\mu g\ ml^{-1}$)	1.06	1.33	1.02	0.93	1.43	0.7
Limit of quantification (LOQ) ($\mu g\ ml^{-1}$)	3.53	4.44	3.40	3.11	4.78	2.12
Regression equation**:						
Slope (b)	0.1486	0.1736	0.0153	0.1634	0.226	0.0221
Intercept (a)	0.0059	0.0328	-0.0034	-0.0451	0.028	0.029
Correlation coefficient (r)	0.9999	0.9995	0.9998	0.9997	0.9997	0.9999
SE	0.33	0.44	0.28	0.31	0.52	0.2
Reproducibility (R. S. D%)	1.27	0.64	0.94	0.67	0.51	0.99
Repeatability (R. S. D %) Molar absorptivity (L mol-1cm-1)	1.38 $1.5*10^3$	1.1 $1.8*10^3$	1.2 $1.5*10^3$	1.6 $1.6*10^3$	0.69 $2.4*10^3$	1.2 $2.3*10^3$

Table 2: Determination of Terbinafine HCl, Telmisartan and Ramiprilusing cerium(IV) sulphate and cerium(IV) sulphate-chromotrope 2R

	Cerium(IV) sulphate method						Cerium(IV) sulphate + C2R method					
	Terbinafine HCl		Telmisartan		Ramipril		Terbinafine HCl		Telmisartan		Ramipril	
	Taken μg ml^{-1}	Recovery* %	Taken μg ml^{-1}	Recovery* %	Taken μg ml^{-1}	Recovery* %	Taken μg ml^{-1}	Recovery* %	Taken μg ml^{-1}	Recovery* %	Taken μg ml^{-1}	Recovery* %
	1	98.32	1	98.62	10	100.26	1	99.39	1	98.23	10	100.00
	2	98.96	1.5	99.92	30	98.78	2	99.36	2	100.00	20	99.77
	3	100.96	3.5	99.93	40	100.23	3	101.67	3	100.59	30	99.70
	4	100.29	4	101.84	60	100.59	4	100.4	4	100.88	40	100.79
	5	100.28	4.5	99.49	70	99.29	5	100.8	5	99.29	50	99.64
	6	100.39	5	99.33			6	100				
	7	99.41					7	99.3				
Mean±S.D.	99.8±0.93		99.86±1.09		99.83±0.76		100.13±0.823		99.8±1.07		99.98±0.47	
N	7		6		5		7		5		5	
S.D.	0.93		1.09		0.76		0.823		1.07		0.47	
R.S.D.	0.94		1.09		0.76		0.82		1.07		0.47	
V	0.87		1.2		0.58		0.79		1.14		0.18	
S.E.	0.35		0.44		0.34		0.31		0.48		0.21	

* Average of three experiments

Table 3: Precision of the proposed methods for analysis of Terbinafine HCl, Telmisartan and Ramipril

	Drug	Terbinafine HCl	Telmisartan	Ramipril	Terbinafine HCl	Telmisartan	Ramipril
	Method	Cerium (IV) sulphate method	Cerium (IV) sulphate + C2R method				
	Wavelength (nm)	319 nm	319 nm	319 nm	507 nm	507 nm	507 nm
	Weight taken (μg/ml)	2	1.5	40	3	1	10
	Validation Parameters						
	%Recovery						
	Experiment						
Intra-day	1	99	100	99	101	101	102
	2	102	101	97	102	100	100
	3	101	100	99	100	100	101
	4	99	100	100			102
	5	100	101				
	Mean	100	101	99	101	101	101
	S.D.	1.28	0.64	1.18	0.67	0.51	1
	R.S.D.	1.27	0.64	1.19	0.67	0.51	0.99
Inter-day	%Recovery						
	Experiment						
	1	99	98	99	99	98	99
	2	100	101	97	98	97	98
	3	99	100	99	101	97	100
	4	102	100				
	Mean	100	99	98	99	98	99
	S.D.	1.38	1.1	0.92	1.59	0.68	1.1
	R.S.D.	1.38	1.1	.94	1.6	0.69	1.2

Table 4: Statistical data for determination of Terbinafine HCl, Telmisartan and Ramipril using ceric (IV) sulphate and ceric (IV) sulphate-chromotrope 2R

Drug	Parameters	ceric(IV) sulphate method	ceric(IV) sulphate+ C2R method	Reference method
Terbinafine HCl	Mean ±S.D	99.80±0.93	100.13±0.82	100.60±0.96[50]
	N	7	7	5
	Variance	0.87	0.79	0.92
	Student-t-test	1.45 (2.228)*	0.87 (2.228)*	
	F-test	1.06 (4.53)*	1.16 (4.53)*	
Telmisartan	Mean ±S.D	99.86±1.1	99.80±1.07	99.99±1.02[51]
	N	6	5	4
	Variance	1.2	1.14	1.03
	Student-t-test	0.19 (2.306)*	0.27 (2.365)*	
	F-test	1.17 (6.41)*	1.11 (6.69)*	
Ramipril	Mean ±S.D	99.83±0.76	99.98±0.47	100.17±0.86[52]
	N	5	5	5
	Variance	0.58	0.18	0.74
	Student-t-test	0.66 (2.306)*	0.44 (2.306)*	
	F-test	1.28 (6.39)*	4 (6.39)*	

*Tabulated values of t and F at p = 0.05

Table 5: Application of standard addition technique for determination of Terbinafine HCl, Telmisartan and Ramiprilin their pharmaceutical formulations using cerium(IV) sulphate

	Terbinafine HCl (Lamisil tablets)			Telmisartan (Micardis tablets)			Ramipril (Tritace Protect tablets)		
	Taken	Added	Recovery*	Taken	Added	Recovery*	Taken	Added	Recovery*
	μg ml^{-1}		%	μg ml^{-1}		%	μg ml^{-1}		%
	1	--	98.32	1	--	99.19	10	--	100.26
		1	98.99		0.5	99.31		20	99.15
		2	98.28		1	99.77		30	100.96
		4	97.93		1.5	98.77		50	99.79
		5	97.19		2	99.42		60	98.41
					3	98.54			
					3.5	99.11			
Mean±S.D.	98.4±0.66			99±0.41			99.71±0.98		
N	4			6			4		
V	0.43			0.17			0.97		
S.D.	0.66			0.41			0.98		
S.E.	0.33			0.17			0.49		

* Mean of three different experiments

Table 6: Application of standard addition technique for determination of Terbinafine HCl, Telmisartan and Ramipriin their pharmaceutical formulations using cerium(IV) sulphate-chromotrope 2R

	Terbinafine HCl (Lamisil tablets)			Telmisartan (Micardis tablets)			Ramipril (Tritace Protect tablets)		
	Taken	Added	Recovery*	Taken	Added	Recovery*	Taken	Added	Recovery*
	μg ml^{-1}		%	μg ml^{-1}		%	μg ml^{-1}		%
	2	--	99.48	1	--	98.24	10	--	97.74
		2	99.48		1	97.36		10	97.74
		3	98.96		1.5	97.80		20	96.38
		4	98.70		3	100.29		25	97.01
		5	100.99		4	98.35		30	95.93
Mean±S.D.	99.52±0.89			97.96±0.52			96.96±0.81		
N	4			4			4		
V	0.79			0.27			0.65		
S.D.	0.89			0.52			0. 81		
S.E.	0.44			0.26			0.4		

* Mean of three different experiments

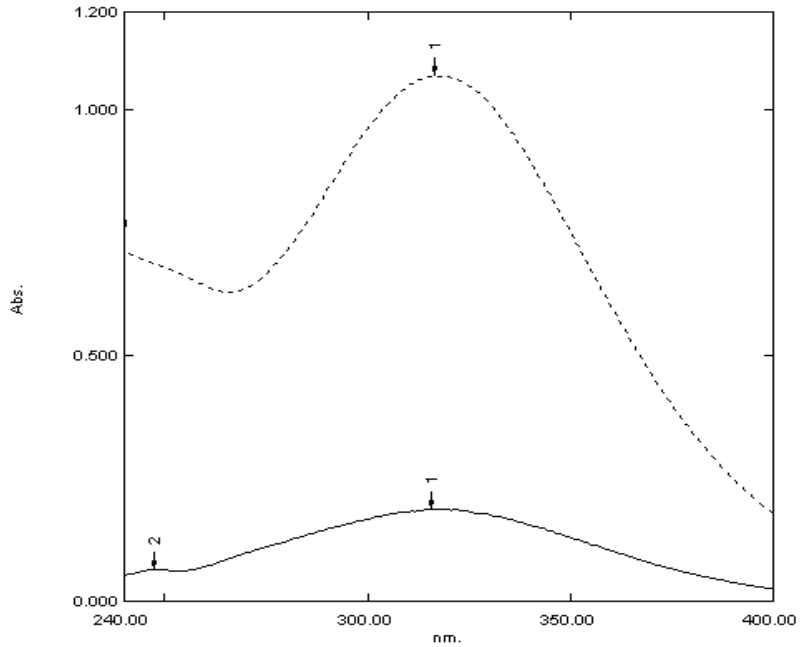


Fig. 2: Absorption spectra of the reaction of Ce (IV) sulphate with 50 µg ml^{-1}Terbinafine HCl(——)and Blank(- - - - -)

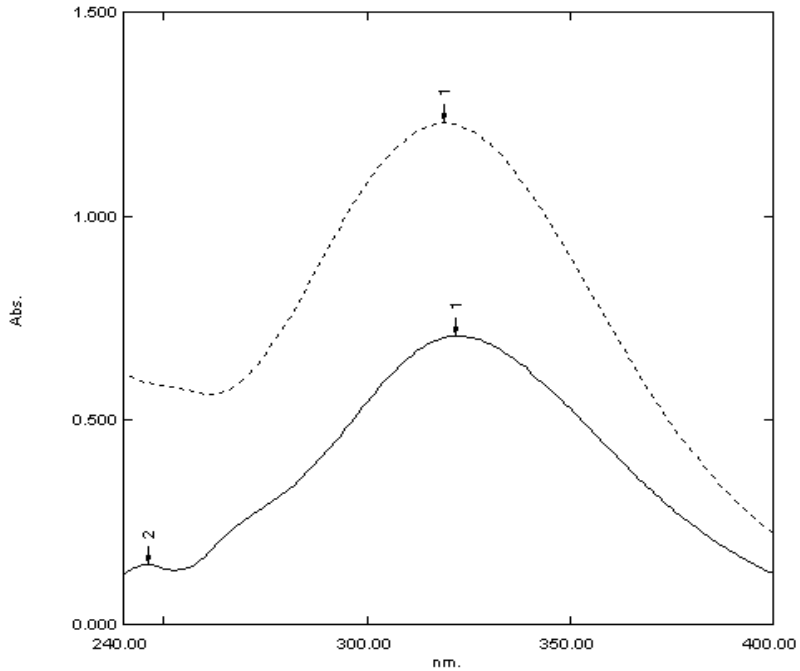


Fig. 3: Absorption spectra of the reaction of Ce (IV) sulphate with 100µg ml^{-1}Telmisartan(——)and Blank (- - - -)

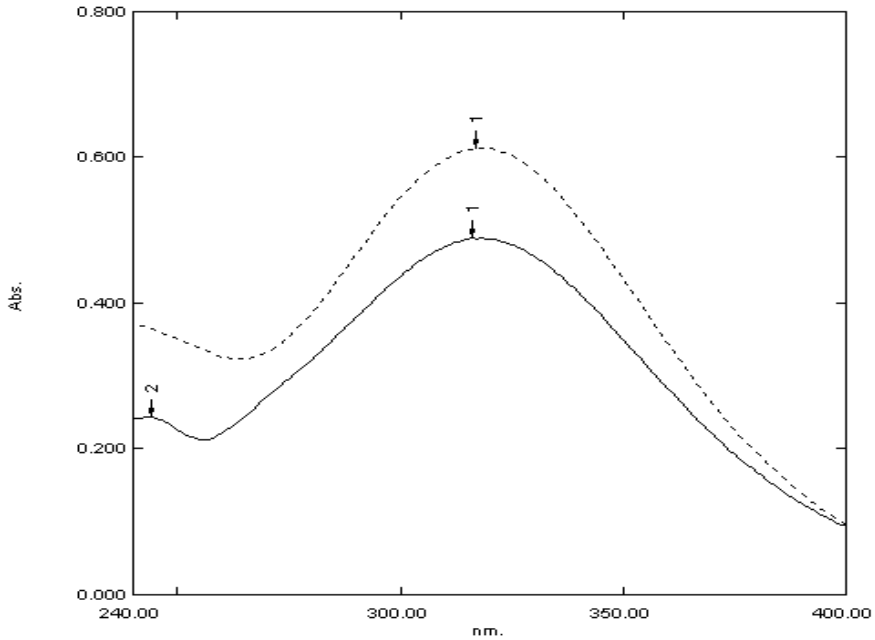


Fig. 4: Absorption spectra of the reaction of Ce(IV) sulphate with 50 µg ml^{-1}Ramipril (——)and Blank (- - - -)

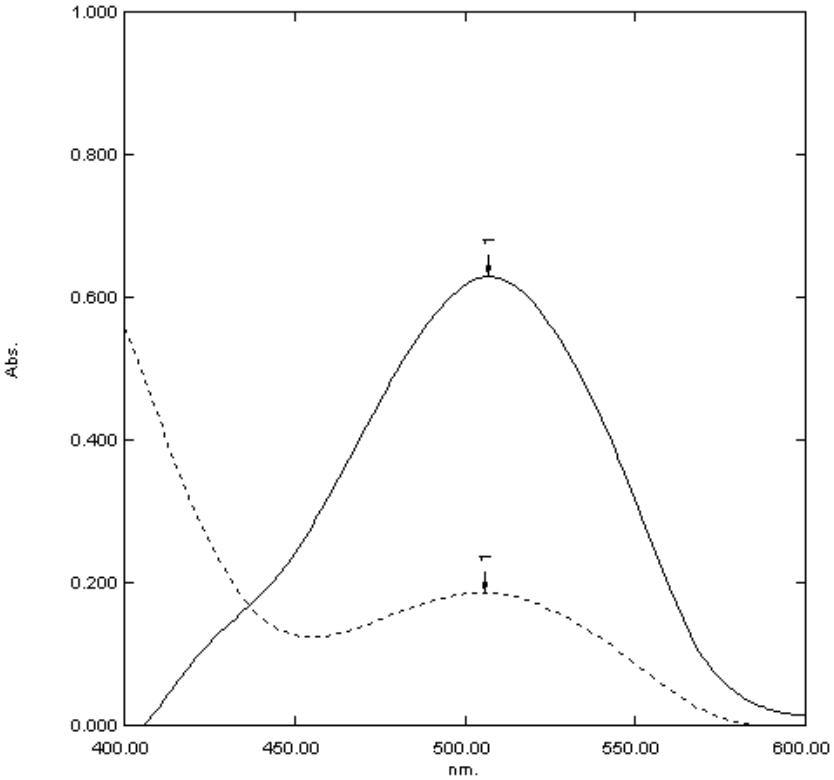


Fig. 5: Absorption Spectra of the reaction products of Cerium (IV) sulphate and C2R with 50 µg ml^{-1}Terbinafine HCl(——) and Blank (- - - -)

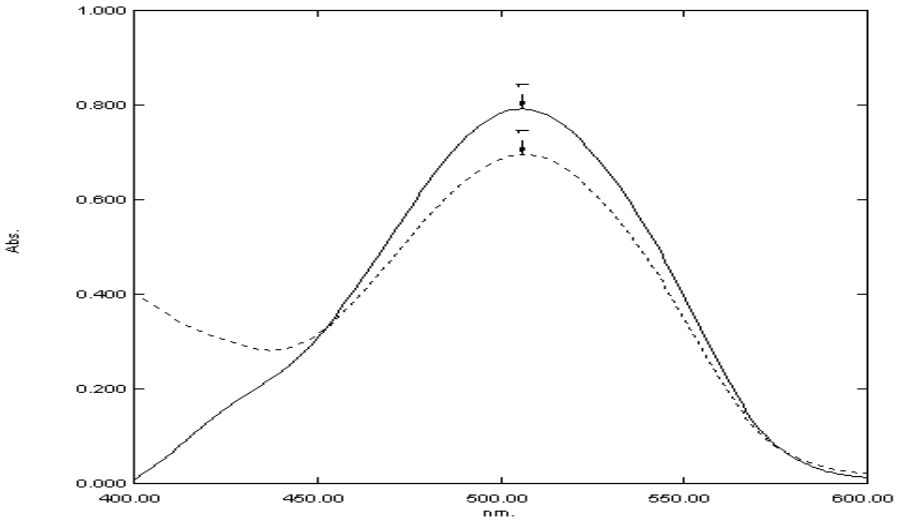


Fig. 6: Absorption Spectra of the reaction products of Cerium (IV) sulphate and C2R with 100 µg ml^{-1}Telmisartan(——) and Blank (- - - -)

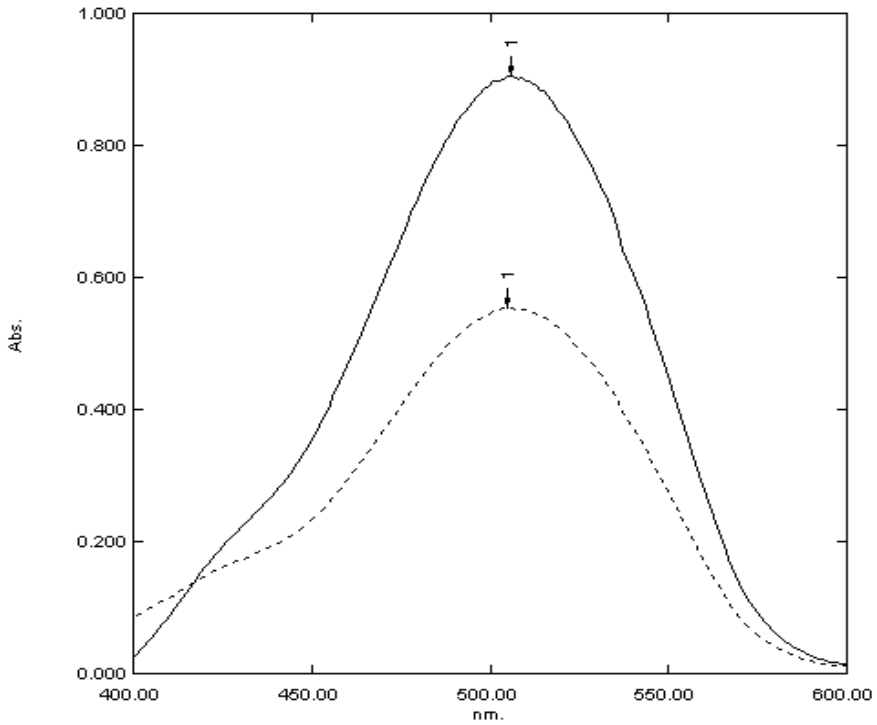


Fig. 7: Absorption Spectra of the reaction products of Cerium (IV) sulphate and C2R with 50 µg ml^{-1}Ramipril(——)and Blank (- - - -)

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