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Research Article

SPECTROPHOTOMETRIC DETERMINATION OF TERBINAFINE HCL AND TELMISARTAN USING POTASSIUM PERMANGANATE

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ABSTRACT

Rapid, simple and validated spectrophotometric method has been described for the assay of Terbinafine HCl and Telmisartan either in pure form or in pharmaceutical formulations. The proposed method was based on the oxidation of the studied drugs by known concentration of potassium permanganate in alkaline medium, the increase in absorbance of coloured manganate ions was measured at 610 nm. Different variables affecting the reaction were studied and optimized. The calibration graphs were linear in the concentration ranges of 2-16µgml^{-1} and 40-128µgml^{-1} for Terbinafine HCl and Telmisartan, respectively. The proposed method was applied successfully for determination of the examined drugs either in a pure or pharmaceutical dosage forms with good accuracy and precision. The results obtained were in good agreement with those obtained using the reference method.

Keywords: Spectrophotometry; Terbinafine HCl and Telmisartan; potassium permanganate.

INTRODUCTION

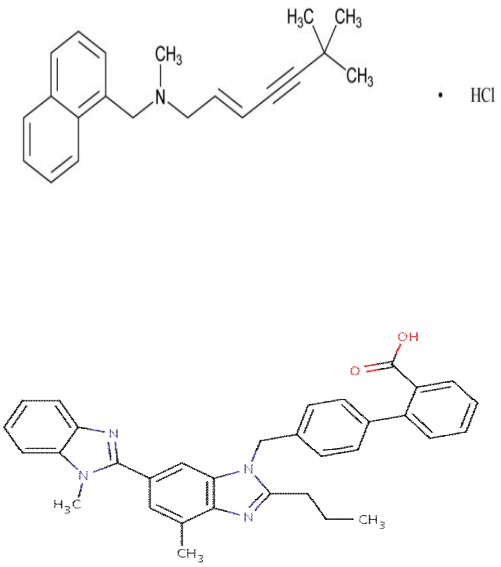
Terbinafine hydrochloride, (TH) (2E)-N, 6, 6-Trimethyl-N-(naphthalen-1- yl methyl)hept-2-en-4- yn-1- amine hydrochloride[1](Figure 1). TH is a synthetic allyl amine antifungal. It is highly lipophilic in nature and tends to accumulate in skin, nails, and fatty tissues. Like other allylamines, terbinafine inhibits ergosterol synthesis by inhibiting the fungal squalene mono-oxygenase (squalene 2, 3-epoxidase), an enzyme that is part of the fungal cell wall synthesis pathway[2,3].

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. Astability-indicating HPTLC[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 oral tablets and topical creams by HPLC[19, 20].

Telmisartan, (TEL) is 4'-[(1, 4'-dimethyl-2'-propyl [2, 6'-bi-1H-benzimidazol]-1'-yl) methyl]-[1, 1'-biphenyl]-2-carboxylic acid[1] (Figure 1). It is indicated in the treatment of essential hypertension[2].

Several methods were reported for determination of Telmisartan either alone or in combination with other drugs. These methods include spectrophotometry[21-27] involving UV first order derivative spectrophotometry[21] and chromatographic methods[28-34] have been reported for determination of Telmisartan alone and in combination with other drugs, involving RP-HPLC for determination of Telmisartan in combination with other drugs[28-30], determination of Telmisartan and forced degradation behavior by Rp-Hplc[31], in human plasma using liquid chromatography tandem mass spectrometry[32], simultaneous estimation of Telmisartan using HPTLC method[33] and first-

derivative, ratio derivative spectrophotometry, TLC-densitometry and spectrofluorimetry[34] methods.



Terbinafine hydrochlorideTelmisartan
Fig. 1: Chemical structure of TH, TEL.

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 REAGENTS

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

1. Terbinafine HCl (Novartis, Egypt).
2. Telmisartan (Boehringer, Egypt).
3. Potassium permanganate: A stock solution of 2.0 × 10^{-2} M $KMnO_4$ (Aldrich, Germany) wasfreshly prepared by dissolving 3.161 g of $KMnO_4$ in boiled and cooled distilled water then completed to the markin a 100 mlcalibratedflask, standardized as recommended and kept in a dark bottle[35]. 7.0 × 10^{-3} M and 1.0× 10^{-2} M solutionsof $KMnO_4$ were prepared by diluting the previousstock solution with distilled water.

III. Standard drug solutions

1. 0.01gm of Terbinafine HCl was dissolved in distilled water in 100ml volumetric flask to obtain working standard solution of concentration 100μgml^{-1}.
2. 0.08 gm of Telmisartan dissolved in 25 ml 0.2M NaOH, then further dilution with 0.2M NaOH to obtain working standard solution of concentration 800μg 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.

V. General procedures

1- Construction of calibration curves

Take different aliquots of standard solutions containing (2-16)and (40-128) μg/ml of Terbinafine HCl and Telmisartan, respectively.For Terbinafine HCl,1.6 ml of 0.9M NaOH, then 2.2ml of 7.0 × 10^{-3} M$KMnO_4$solution were added. These mixtures were kept for 35 minutes at room temperature then measure absorbance at 609 nm against a blank solution simultaneously prepared.In case of Telmisartan, 1.8 ml of 1.0× 10^{-2} M $KMnO_4$ solution was added directly without addition of NaOH; because the drug was dissolved in 0.2 M NaOH and this concentration is enough for the reaction.The mixtures were heated at 85°c for 30minutes. The test tubes were then cooled to room temperature 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 then measure absorbance at 610 nm. Toobtain the standard calibration curves, plot the values ofabsorbance against the drug concentration in μg/ml.

2- Assay of pharmaceutical preparations

a. Lamisil ® tablets

Ten tablets weighed and powdered. A quantity of powdered tablets 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 100 μgml^{-1}.

b. Micardis ® tablets

Ten tablets weighed and powdered. A quantity of powdered tablets equivalent to 20 mg of Telmisartan was shaken with cold water for 2 minutes 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 0.2 M NaOH then filtered and completed to the mark with 0.2M NaOH. Further dilution was made to obtain working solution of the concentration 800μgml^{-1} using0.2 M NaOH.
Standard addition technique was used for analysis of the selected drugs in their commercial tablets (a, b), table (3).

VI.RESULT AND DISCUSSION
The reaction between the selected drugsand $KMnO_4$ in alkaline mediumyields green colour due to of the formation of manganateion (MnO_4^{-2}) with λ max610 nm, figure (2). At this wavelength, all the parameters affecting the development and stability of the reaction product were optimized.

6.1. Investigation of assay parameters
6.1.1. Effect of time
For THreaction with permanganate in alkaline medium, absorbance increasegradually andreach maximum after 30 min., remain stable up to 40 min., then start to decrease, figure (3).In case of TEL,the oxidation reaction of TEL was catalyzed by heating inwater bath at 85°C for 30 minto obtain the highest and most stable absorbance,figure (4, 5).

6.1.2. Effect of $KMnO_4$ concentration and volume
The reaction rate and absorbance increases with increasing $KMnO_4$ concentration. The absorbance was studied in the range2× 10^{-3} to 3× 10^{-2} mol L^{-1} keeping all other parameterconstant. It was found that 7 × 10^{-3} mol L^{-1} $KMnO_4$ is theoptimum concentration for THand 1×10^{-2} mol L^{-1} $KMnO_4$ is theoptimum concentration for TEL. The effect of the colour development was investigatedby adding different volumes (1.2–2.8 ml) of 7× 10^{-3} mol L^{-1}potassium permanganate forTH and (1.2–2.4ml) of 1× 10^{-2} molL^{-1}potassium permanganate for TEL. The maximum absorbanceof the green color was attained with 2.2 ml of the reagent for TH and 1.8 ml for TEL, figure (6, 7).

6.1.3. Effect of NaOH concentration
1.6 ml of 0.9 M NaOH gave maximum colour intensity in case of TH while TELis dissolved in 0.2 M NaOH and this concentration is enough for the reaction, figure (8, 9).

6.1.4. Effect of order of addition
The sequence of addition of reactants was very important. Addition of drug (TH) followed by NaOH and then $KMnO_4$ was recommended to obtain high colour intensity, table (1).

VII. Validation of the proposed methods
Linearity
The method was 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 2. The table also shows the results of the statistical analysis of the experimental data, such as slopes, intercepts, correlation coefficients obtained by the linear least-squares treatment of the results and Molar absorptivity. Results of recovery studies with pure drugs by the proposed method, show small values of standard deviation and variance,table 3, 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 be measured according to ICH recommendation[35] below which the calibration graph is non linear. The results are shown in Table 2. 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 2.
LOQ and LOD were calculated according to the following equations[37]

$$\mathbf{LOQ = 10\ Sa/b}$$
$$\mathbf{LOD = 3.3\ Sa/b}$$

Where Sa is the standard deviation of the blank, and b is the slope of the regression line.

Precision
The precisions of the assays (intra-day and inter-day) were determined for the studied drugs concentrations cited in Table 4, the assays gave satisfactory results. Intra-day precision was assessed by analyzing sample of one concentration three times during a day. The same was done for inter-day precision test except that the sample was analyzed every day for threeconsecutive days.
This level of precision of the proposed methods was adequate for the quality control analysis of TH and TEL.

Accuracy
To test the validity of the proposed method,it is applied for determination of pure samples of the studied drugs over the concentration ranges cited in Table 3. The results obtained were in good agreement with those obtained using the

reference methods[38, 39]. 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 5).

Analytical applications

The results obtained by applying the proposed methods for the determination of drugs in there pharmaceutical formulations (Lamisil and Micardis tablets), Table 6suggest satisfactory results and good % recoveries of the drugs byapplying standard addition technique to check the validity of the method. Hence, these methods can be recommended in routine analysis of TH and TEL.

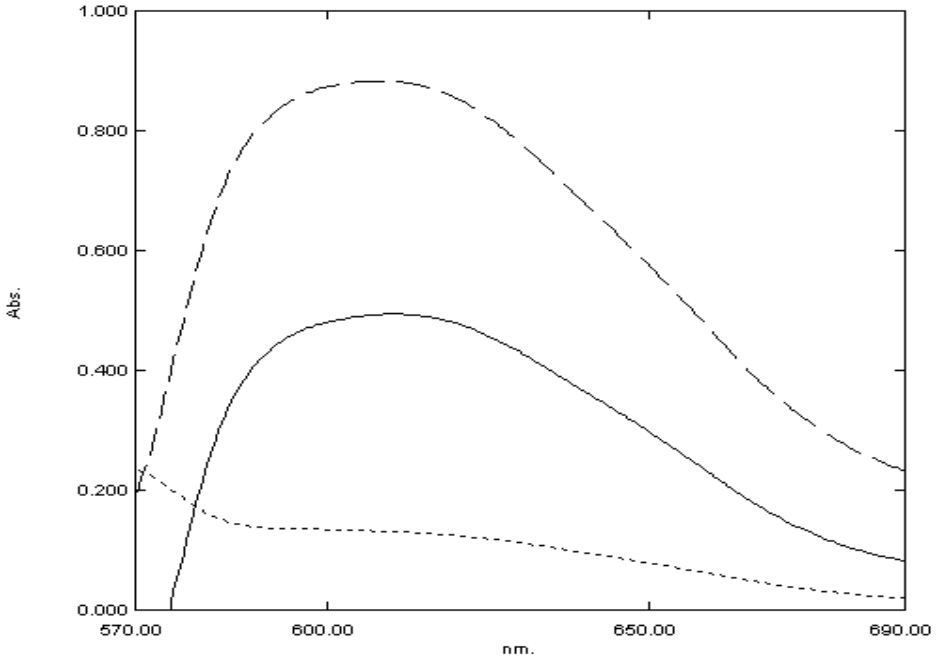


Fig. 2: Absorption spectra of the reaction of $KMnO_4$with:
- **10 µg ml^{-1} Terbinafine HCl (—)**
- **120 µg ml^{-1}Telmisartan(— —)and blank (- - - -).**

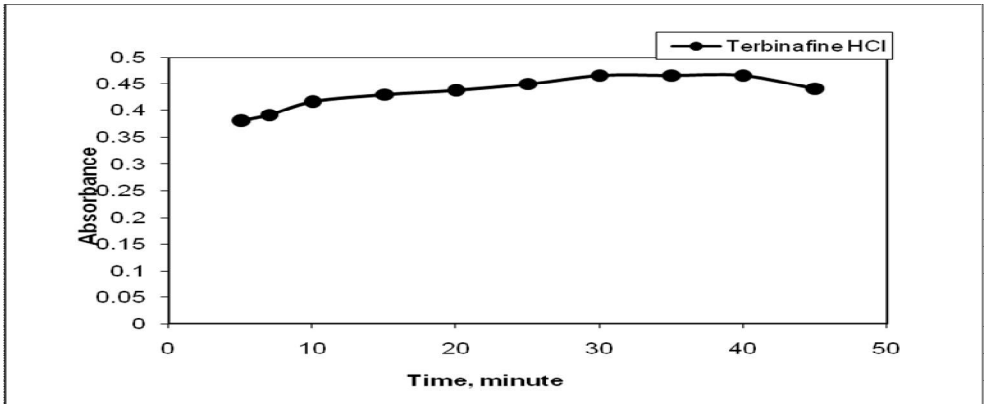


Fig. 3: Effect of time on absorbance stability of 8 µg ml^{-1}TerbinafineHCl

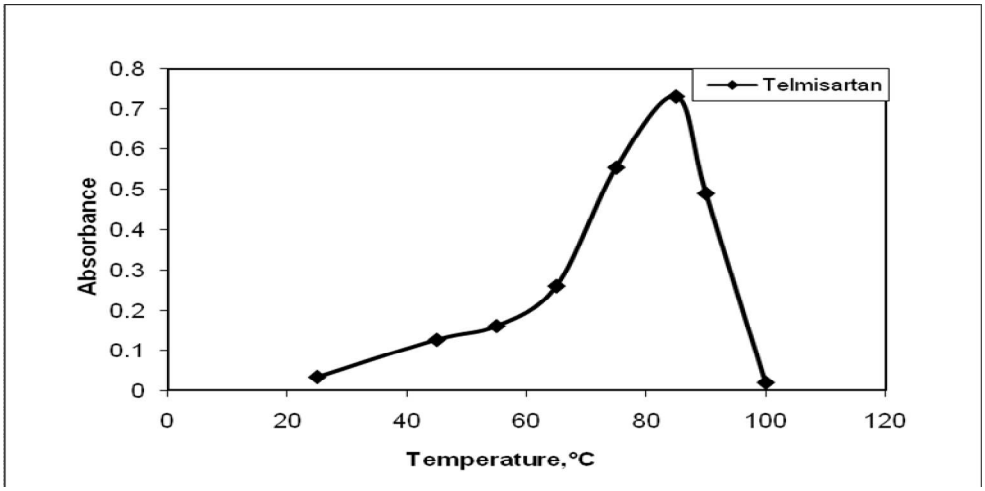


Fig. 4: Effect of temperature on absorbance of Telmisartan

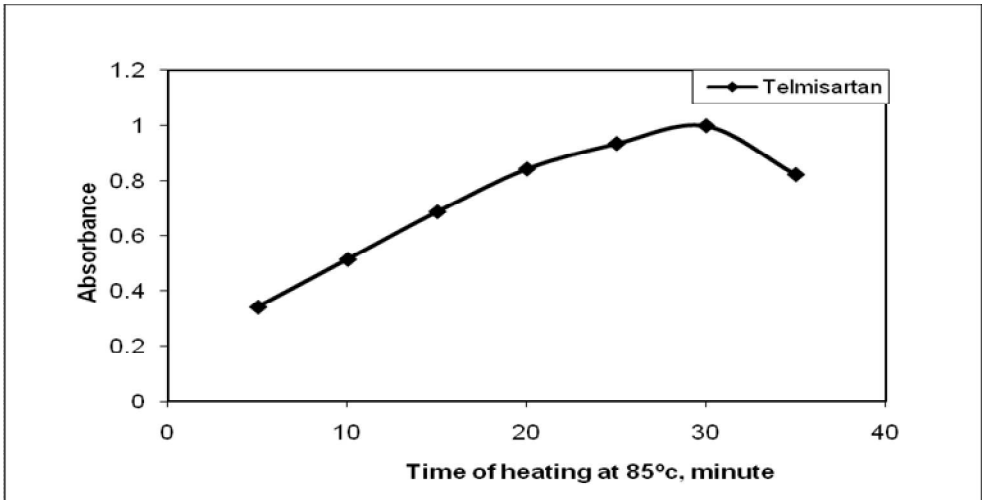


Fig. 5: Effect of heating time at 85°c on absorbance of Telmisartan

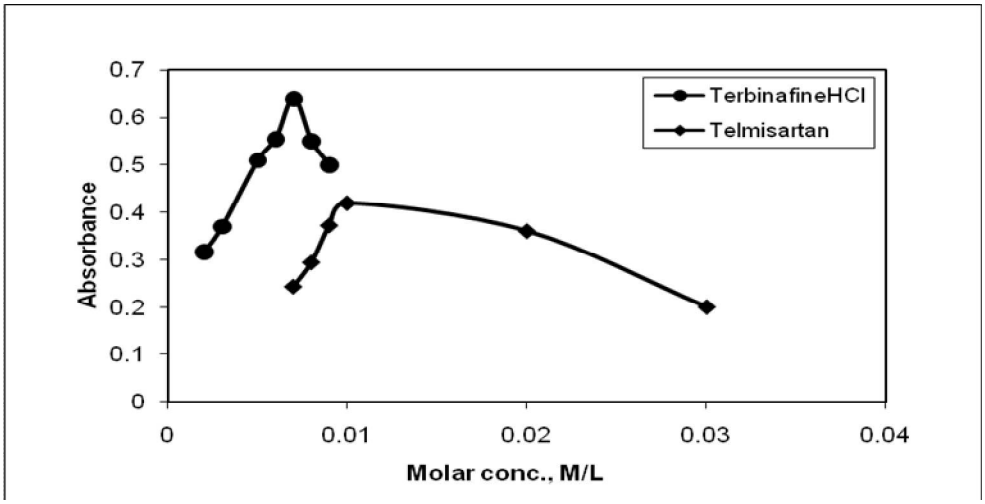


Fig. 6: Effect of $KMnO_4$ molar concentration on absorbance of 12 µgml^{-1} Terbinafine HCl and 48µgml^{-1} Telmisartan.

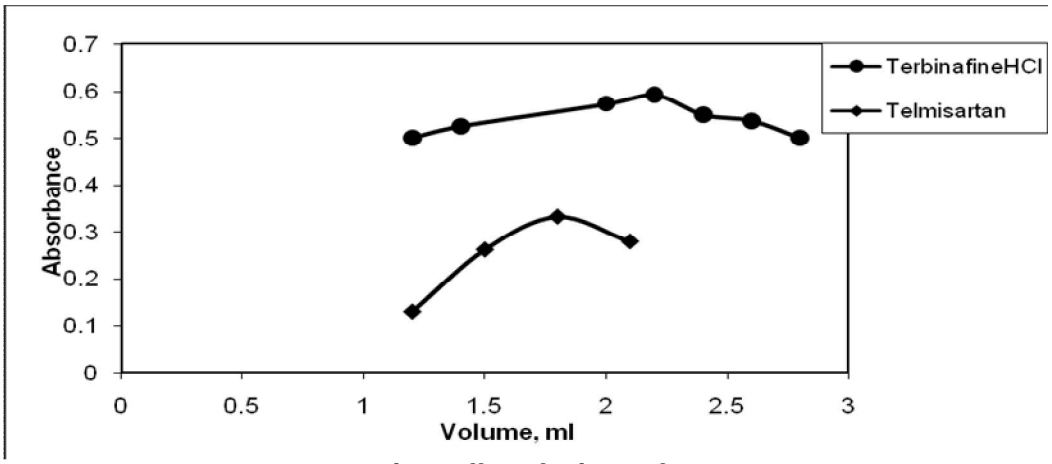


Fig. 7: Effect of volume of:
(a)7.0 × 10^{-3} M $KMnO_4$on absorbance of 12µgml^{-1} Terbinafine HCl
(b) 1×10^{-2}M $KMnO_4$ on absorbance of 48µgml^{-1} Telmisartan

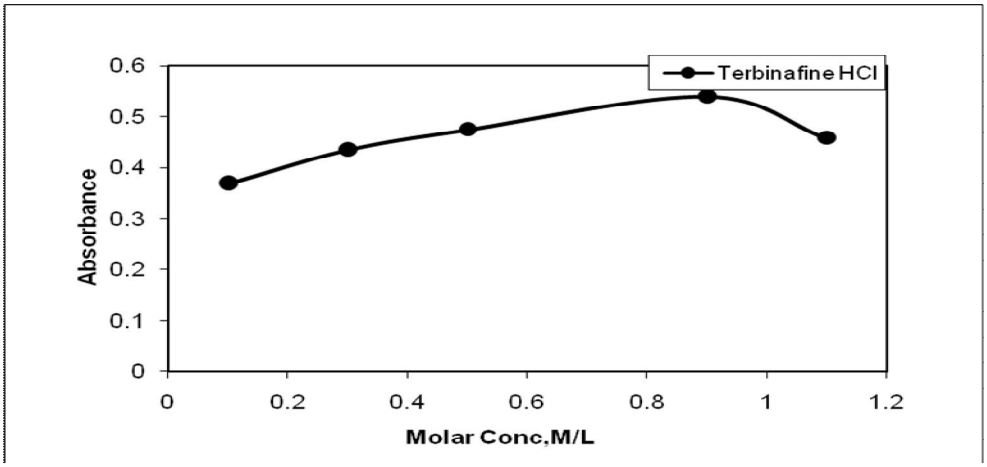


Fig. 8: Effect of NaOH molar concentration on absorbance of 1µgml^{-1} Terbinafine HCl

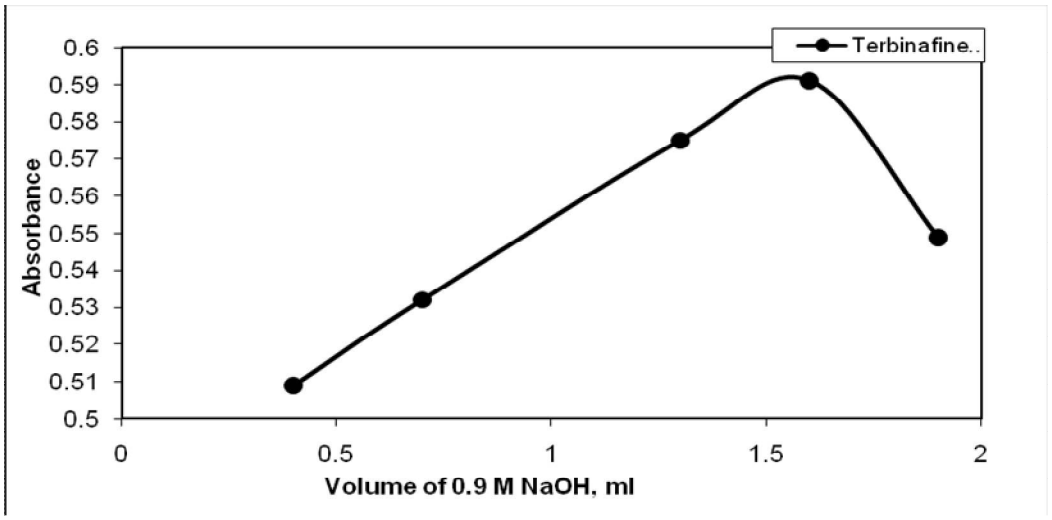


Fig. 9: Effect of volume of 0.9 M NaOH on absorbance of 10µgml^{-1} Terbinafine HCl

Table 1: Effect of order of addition of NaOH and $KMnO_4$ to 10µgml^{-1}TH

Condition (order of addition)	Absorbance at 609 nm
1- TH+ NaOH+ $KMnO_4$	0.59
2- TH+ $KMnO_4$+ NaOH	0.39

Table 2: Spectral data for determination of Terbinafine HCl and Telmisartan using the proposed method

Parameters	Terbinafine HCl	Telmisartan
Linearity range (µg ml^{-1})	2-16	40-128
Wavelength (nm)	609	609
Limit of detection (µg ml^{-1})	0.65	13
Limit of quantification(µg ml^{-1})	1.96	39.3
Regression equation**:		
Slope (b)	0.0509	0.007
Intercept (a)	0.0238	0.0494
Correlation coefficient (r)	0.9999	0.9996
SE	0.36	0.37
Reproducibility (R.S.D%)	0.7	1.23
Repeatability (R.S.D %)	0.62	1.56
Molar absorptivity (L mol-1cm-1)	$1.8 \cdot 10^4$	$3.97 \cdot 10^3$

** A=a + bc

Table 3: Determination of Terbinafine HCl and Telmisartan using the proposed method

Drug	Terbinafine HCl		Telmisartan	
Parameters	Taken µg ml^{-1}	Recovery* %	Taken µg ml^{-1}	Recovery* %
	2	98.43	40	98.79
	4	100.79	48	101.37
	8	99.75	80	100.64
	12	100.88	96	99.64
	14	100.08	112	101.10
	16	99.73	128	99.84
Mean±S.D.	99.94±0.89		100.23±0.89	
N	6		6	
S.D.	0.89		0.89	
R.S.D.	0.89		0.89	
V	0.8		0.96	
S.E.	0.36		0.37	

* Average of three experiments

Table 4: The intra-day and inter-day accuracy and precision data for Terbinafine HCl and Telmisartan obtained using the proposed method

	Drug	Terbinafine HCl	Telmisartan
	Wavelength(nm)	609	609
	Weight taken (µg/ml)	14	80
	Validation Parameters / % Recovery Experiment		
Intra-day	1	98.68	101.18
	2	99.38	101.18
	3	97.98	99.04
	Mean	98.68	100.46
	S.D.	0.70	1.24
	R.S.D.	0.71	1.23
	% Recovery Experiment		
Inter-day	1	98.96	101.18
	2	99	100.82
	3	97.98	98.32
	Mean	98.68	100.11
	S.D.	0.61	1.56
	R.S.D.	0.62	1.56

Table 5: Statistical data for determination of Terbinafine HCl and Telmisartan using the proposed method compared against reference one

Drug		Proposed method	Reference method
Terbinafine HCl	Mean ±S.D	99.94±0.89	101±0.96[38]
	N	6	5
	Variance	0.80	0.92
	Student-t-test	1.899 (2.262)*	
	F-test	1.15 (3.26)*	
Telmisartan	Mean ±S.D	100.23±0.89	100±1.02[39]
	N	6	4
	Variance	0.96	1.03
	Student-t-test	0.359 (2.306)*	
	F-test	1.073 (9.01)*	

*Theoretical values of t and F at p = 0.05.

Table 6: Application of standard addition technique for determination of Terbinafine HCl and Telmisartan in their pharmaceutical formulations using the proposed method

	Terbinafine HCl (Lamisil® tablets)			Telmisartan (Micardis® tablets)		
	Taken	Added	Recovery*	Taken	Added	Recovery*
	µg ml^{-1}		%	µg ml^{-1}		%
	2	--	98.43	40	--	97.36
		2	100.39		40	99.50
		3	99.67		52	98.52
		5	98.70		64	98.35
		7	98.85		68	98.45
		8	98.04		72	96.94
		12	97.61			
Mean±S.D.	99±0.95			98.19±0.91		
N	6			5		
V	0.90			0.83		
S.D.	0.95			0.91		
S.E.	0.39			0.37		

*Mean of three different experiments

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