



FIRST ORDER DERIVATIVE SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND CHLORTHALIDONE IN BULK AND PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A simple, precise, and accurate method was developed for the estimation of Telmisartan (TEL) and Chlorthalidone (CHL) in bulk and pharmaceutical dosage form using first order derivative spectrophotometry. Wavelength selected for quantitation were 264.85nm for Telmisartan (zero crossing point of Chlorthalidone) and 222.38nm for Chlorthalidone (zero crossing point of Telmisartan). The method was validated with respect to linearity, accuracy, precision, limit of detection and limit of quantitation in accordance with the International Conference on Harmonisation (ICH) guidelines. Linearity was observed in concentration range of 8-48 µg/ml for Telmisartan and 2.5-15 µg/ml for Chlorthalidone. The limit of detection and limit of quantitation were found to be 0.234µg/ml and 0.712 µg/ml for Telmisartan and 0.102 µg/ml and 0.309 µg/ml for Chlorthalidone. The percentage recovery of Telmisartan and Chlorthalidone was found to be 99.26% and 99.36% respectively. The % R.S.D. values for intra-day and inter-day precision study were <1.0%, confirming that the method was sufficiently precise. The method can be successfully employed for the simultaneous estimation of Telmisartan and Chlorthalidone in pharmaceutical formulations.

Keywords: Telmisartan, Chlorthalidone, Derivative spectrophotometry, First order, Validation

INTRODUCTION

Telmisartan(TEL) is an Angiotensin II receptor antagonist used as an antihypertensive drug. Chemically it is 4'-[[4-methyl-6-(1-methyl-2-benzimidazolyl)-2-propyl-1-benzimidazolyl]methyl]-2-biphenylcarboxylic acid (Figure 1)^{1,2}. Chlorthalidone(CHL) is diuretic drug used in treatment of hypertension in combination with Telmisartan. CHL is chemically (RS)-2-chloro-5-(1-hydroxy-3-oxoisindolin-1-yl) benzenesulphonamide (Figure2)^{1,2}. TEL and CHL both are official in IP³, BP⁴ and USP⁵. TEL is estimated by Liquid Chromatography as per IP³ and Potentiometric titration as per BP⁴ and USP⁵. The analytical techniques reported for the determination of TEL include HPLC⁶⁻⁸, spectrophotometry⁹⁻¹², HPTLC^{13,14} etc. either separately or in combination with other drugs. CHL is estimated by potentiometric titration as per IP³ and Liquid Chromatography as per BP⁴ and USP⁵. Several analytical method that use liquid chromatography¹⁵⁻¹⁷, spectrophotometry¹⁹ have been reported in the literature for the determination of CHL in pharmaceutical preparation either separately or in combination with other drugs. Literature survey does not reveal any spectrophotometric method for simultaneous determination of TEL and CHL in Pharmaceutical dosage form. The present developed method is simple, precise and accurate for simultaneous determination of both drugs in their Pharmaceutical Dosage forms as per International Conference on Harmonization (ICH) guidelines²⁰.

MATERIALS AND METHOD

Apparatus

Instrument used was an UV-VIS-NIR Spectrometer Perkin Elmer Lambda 19 Range: 185-3200 nm, with a pair of 1 cm matched quartz cells. Calibrated glass wares were used throughout the work.

Reagents and chemicals

Pure drug samples of TEL and CHL were obtained from Alembic Limited, Vadodara, Gujarat. Methanol AR Grade was used as solvent and obtained from Allied Chemical Corporation, Vadodara, Gujarat, India.

Marketed formulation

Combined tablet formulation Eritel- CH40 was procured from local market. Each tablet contains 40 mg Telmisartan and 12.5 mg Chlorthalidone.

Preparation of standard stock solution

Accurately weighed quantity of TEL 10 mg and CHL 10 mg was transferred into two separate 10 ml volumetric flask, dissolved and diluted up to mark with methanol. This will give a stock solution having strength of 1000 µg/ml.

Preparation of working standard solution

5 ml of standard stock solution of TEL (1000 µg/ml) and CHL(1000 µg/ml) was pipette out in to two separate 50 ml volumetric flask and volume was adjusted to the mark with methanol to get 100 µg/ml of TEL and 100 µg/ml of CHL.

Determination of wavelength for measurement

3.2 ml of working standard solution of TEL (100 µg/ml) and 1.0 ml of working standard solution of CHL(100 µg/ml) was pipette out in to 10 ml volumetric flask and volume was adjusted to the mark with methanol to get 32 µg/ml of TEL and 10 µg/ml of CHL. Each solution was scanned between 200-400 nm.

The first order derivative spectra of each solution were obtained. The zero crossing points were found to be 222.38 nm and 264.85 nm for TEL and CHL respectively (figure 3). Wavelengths selected for quantification were 264.85 nm for TEL (zero crossing point for CHL) and 222.38 nm for CHL (zero crossing point for TEL).

Preparation of calibration curve

Calibration curve for TEL

Standard TEL solutions of 8-48 µg/ml were prepared by pipetting out 0.8, 1.6, 2.4, 3.2, 4.0, 4.8 ml of the working standard solution of TEL (100 µg/ml) into series of 10 ml volumetric flasks and the volume was adjusted to the mark. Absorbance of each solution was measured at 264.85 nm using First order derivative spectrophotometry. A calibration curve was prepared by plotting absorbance against respective concentration (Figure 4).

Calibration curve for CHL

Standard CHL solutions of 2.5-15 µg/ml were prepared by pipetting out 0.25, 0.5, 0.75, 1, 1.25 and 1.5 ml of the working standard solution of CHL (100 µg/ml) into series of 10 ml volumetric flasks and the volume was adjusted to mark with methanol. Absorbance of each solution was measured at 222.38 nm using First order derivative spectrophotometry. A calibration curve was obtained by plotting absorbance against respective concentration (Figure 5).

Development and validation of method

Linearity and range

Aliquots of working standard solutions of TEL and CHL were taken in 10 ml volumetric flasks and diluted with methanol to get final concentrations in range of 8-48 µg/ml for TEL and of 2.5-15 µg/ml of CHL. This calibration range was prepared six times and absorbances were measured at respective wavelengths for each drug separately.

Precision

Precision of the method was determined by performing interday variation and intraday variation (%RSD). Intra-day precision (%RSD) was assessed by analyzing standard drug solutions within the calibration range, three times on the same day. Inter-day precision (%RSD) was assessed by analyzing drug solutions within the calibration range on three different days over a period of 7 days.

Repeatability

For repeatability study, 32 µg/ml of TEL and 10 µg/ml concentration of CHL were measured six times.

Recovery studies

To study the accuracy of the proposed method, recovery studies were carried out by standard addition method at three different levels (80%, 100%, 120%). A known amount of drug was added to pre analyzed sample powder and percentage recoveries were calculated.

LOD and LOQ

The LOD and LOQ were calculated by equation. Based on the standard deviation of the response and the slope, LOD and LOQ were estimated using the formulae:

$$\text{LOD} = 3.3 \sigma/S$$

$$\text{LOQ} = 10 \sigma/S$$

Where, σ = the standard deviation of the response, S = the slope of the calibration curve

LOD and LOQ were determined from the standard deviations of the responses for six replicate determinations.

Analysis of TEL and CHL in marketed Tablet Formulation

To determine the content of TEL and CHL simultaneously in conventional tablets (Eritel- CH40 label claim 40 mg TEL and 12.5 mg CHL); twenty tablets were accurately weighed, average weight determined and ground to fine powder. A quantity of powder equivalent to 40 mg TEL and 12.5 mg CHL was transferred into 50 ml volumetric flask containing 40 ml methanol, sonicated for 20 min and diluted to mark with same solvent to obtain 800 µg/ml of TEL and 250 µg/ml of CHL. The resulting solution was filtered using 0.45 µm filter (Millifilter, MA). 1 ml of the above filtrate was diluted to 10 ml with methanol to obtain 80 µg/ml of TEL and 25 µg/ml of CHL. 2 ml of above solution was further diluted to 10 ml with methanol to obtain 16 µg/ml of TEL and 5 µg/ml of CHL. The absorbance of the resulting solution was measured using first order derivative spectrophotometry at 264.85 nm for TEL and 222.38 nm for CHL. The concentration of each drug was calculated using equation of straight line.

Table 1: Result of Calibration readings for TEL

Concentration µg/ml	Absorbance Mean (n=6) ± SD	%RSD
8	0.09622±0.00062	0.651
16	0.17271±0.00057	0.329
24	0.24907±0.00052	0.212
32	0.32141±0.00073	0.227
40	0.40121±0.00051	0.128
48	0.45348±0.00856	0.188

Table 2: Result of Calibration readings for CHL

Concentration µg/ml	Absorbance Mean (n=6) ± SD	%RSD
2.5	0.06735±0.00057	0.846
5	0.13637±0.00082	0.605
7.5	0.19675±0.00064	0.327
10	0.24852±0.00104	0.419
12.5	0.31170±0.00061	0.198
15	0.37125±0.00072	0.195

Table 3: Statistical Data of TEL and CHL

Parameters	Result for TEL	Result for CHL
Linearity Range(µg/ml)	8-48	2.5-15
Slope	0.009	0.024
Intercept	0.027	0.012
Limit of Detection(µg/ml)	0.234	0.102
Limit of Quantitation(µg/ml)	0.712	0.309
Regression Equation	Y=0.009X+0.027	Y=0.024X+0.012
Co-Efficient of Determination (r ²)	0.997	0.998

Table 4: Intra-Day and Inter-Day study of TEL

Concentration (µg/ml)	Intra-Day Abs. Mean (n=3) ± SD	%RSD	Concentration (µg/ml)	Inter-Day Abs. Mean (n=3) ± SD	%RSD
16	0.17212±0.0003	0.214	16	0.17184±0.0002	0.120
24	0.24888±0.0003	0.148	24	0.24872±0.0006	0.276
32	0.32147±0.0013	0.43	32	0.32207±0.0004	0.132

Table 5: Intra-Day and Inter-Day study of CHL

Concentration µg/ml	Intra-Day Abs. Mean (n=3) ± SD	%RSD	Concentration µg/ml	Inter-Day Abs. Mean (n=3) ± SD	%RSD
5	0.1371±0.0005	0.408	5	0.13642±0.0006	0.488
7.5	0.19729±0.0006	0.327	7.5	0.19625±0.0007	0.383
10	0.24837±0.0005	0.229	10	0.24910±0.0004	0.170

Table 6: Repeatability study of TEL and CHL

Concentration	TEL (32µg/ml)	CHL (10µg/ml)
Absorbance	0.32137	0.24869
	0.32278	0.24746
	0.32135	0.24821
	0.32118	0.24989
	0.32056	0.24738
	0.32125	0.24952
Mean	0.32141	0.24852
± SD	0.00073	0.00104
%RSD	0.227	0.419

Table 7: Determination of Accuracy

Concentration of Sample Taken (µg/ml)	Concentration of Pure API spiked (µg/ml)	Total Concentration (µg/ml)	Mean Total Concentration Found (n=3) (µg/ml)	%Recovery Mean (n=3)
TEL 16 µg/ml	12.8	28.8	28.75	99.61
	16	32	31.78	98.63
	19.2	35.2	35.11	99.53
	Avg.		99.26	
CHL 5 µg/ml	4	9	8.964	99.1
	5	10	9.922	99.44
	6	11	10.972	99.53
	Avg.		99.36	

Table 8: Assay Result of Marketed Formulation

Parameters	Eritel CH-40 TAB	
	TEL	CHL
Actual Concentration (µg/ml)	16	5
Concentration Obtained (µg/ml)	15.88	4.98
%Purity	99.3	99.73
%RSD	0.162	0.947
Limit ³	90-110	92.5-107.5

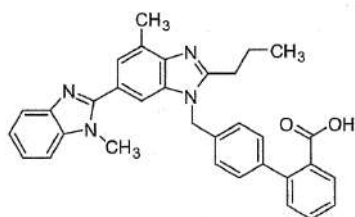


Figure 1: Structure of Telmisartan (TEL)

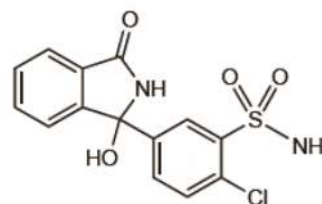


Figure 2: Structure of Chlorthalidone (CHL)

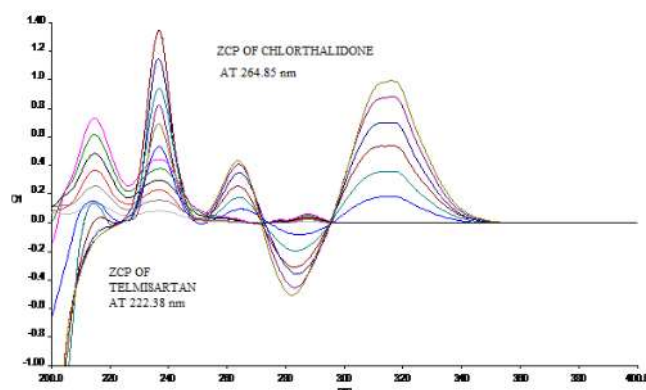


Figure 3: First order derivative overlay of TEL and CHL

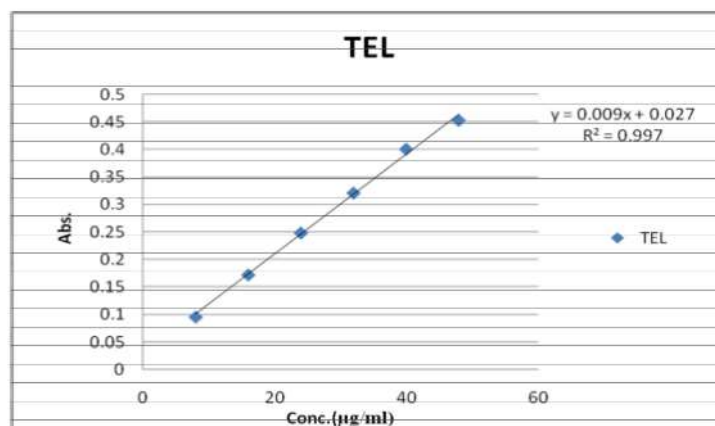


Figure 4: Calibration curve of TEL in Methanol

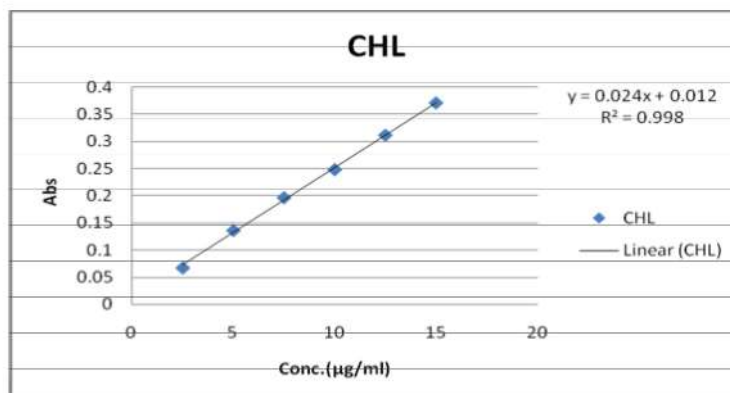


Figure 5: Calibration curve of CHL in Methanol

RESULTS AND DISCUSSION

Validation

Linearity

Linear regression data for the calibration plots revealed good linear relationships between absorbance and concentration over the ranges 8-48 µg/ml for TEL and 2.5-15 µg/ml for CHL. The linear equations for the calibration plots were $y = 0.009x + 0.027$ and $y = 0.024x + 0.012$ with Regression (r^2) being 0.997 and 0.998 for TEL and CHL, respectively (Figure 3,4,5) (Table 1, 2 and 3).

Precision

The precision of the method was expressed as relative standard deviation (RSD %). The %R.S.D. values for intra-day precision study and inter-day study listed in (Table 4 and 5) were <1.0%, confirming that the method was sufficiently precise.

Repeatability

The % RSD for absorbance values of TEL and CHL were found to be 0.227 and 0.419 respectively, as given in Table 6.

Accuracy

When the method was used for accuracy and subsequent analysis of both the drugs from the pharmaceutical dosage form, and spiked with 80, 100, and 120% of additional pure drug, the recovery was found to be 99.26 % for TEL and 99.36 % for CHL (Table 7).

LOD and LOQ

The LOD and LOQ were calculated by equation. The LOD and LOQ values were 0.234 µg/ml and 0.712 µg/ml for TEL and 0.102 µg/ml and 0.309 µg/ml for CHL.

Analysis of TEL and CHL in marketed formulation

When the Eritel CH-40 tablets were analyzed, The % purity was found to be 99.3% for TEL and 99.73% for CHL. (Table 8)

CONCLUSION

The proposed method was developed for the determination of TEL and CHL in the presence of each other. Methods was validated and found to be simple, rapid, sensitive, accurate and precise. The method was successfully used to estimate the amounts of TEL and CHL present in marketed tablet formulation containing TEL and CHL.

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