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RESEARCH ARTICLE

DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND HYDROCHLOROTHIAZIDE IN BULK DRUG AND PHARMACEUTICAL DOSAGE FORM BY UV- SPECTROPHOTOMETRY

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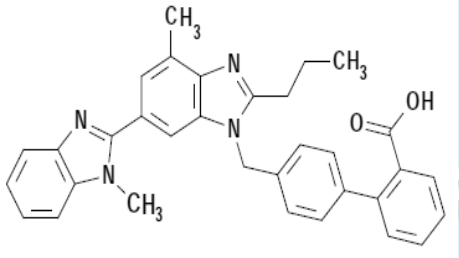
Abstract: A simple, accurate and precise simultaneous analytical method has been developed for simultaneous determination of Telmisartan and Hydrochlorothiazide in bulk drug and tablet dosage form. The wavelength selected for these drugs were 295.5 nm and 273.0 nm respectively. The linearity at selected wavelength lies between 10-90 Âµg/ml for Telmisartan and 5-60 Âµg/ml for Hydrochlorothiazide. The concentrations of these drugs were evaluated in laboratory mixture of reference standard and different marketed formulation. Recovery studies confirmed the accuracy of proposed method. Precision of the method was found as the values within acceptable limit. Thus the proposed method and results were validated as per ICH guidelines. Statistical analysis proves that the method is reproducible and selective for the simultaneous estimation of Telmisartan and Hydrochlorothiazide.

Key words: Telmisartan; Hydrochlorthiazide UV Visible Spectroscopy.

INTRODUCTION:

Telmisartan (TEL) is a non-peptide angiotensin-2 receptor antagonist and a derivative of benzimidazole[1-3]. It is selectively and insurmountably inhibits angiotensin – 2 AT1 receptor subtype without affecting other systems involves in cardiovascular regulation[4,5]. TEL is chemically 2-(4-{[4-Methyl-6-(1-methyl-1*H*-1, 3-benzodiazol-2-yl)-2-propyl-1*H*-1, 3-benzodiazol-1-yl] methyl} phenyl) benzoic acid. Hydrochlorothiazide (HCT) is one of the widely used thiazide diuretic which reduces reabsorption of electrolytes from the renal tubules and chemically 6-chloro-1, 1-dioxo-3, 4-dihydro-2*H*-1, 2, 4-benzothiadiazine-7-sulfonamide. The combination of TEL and HCT is available as tablet dosage form[6-10].

The literature survey revealed that TEL is not yet official in any pharmacopoeia. Several analytical methods have been reported for the determination of TEL in biological fluids and formulation includes HPLC, HPTLC, electrophoretic and fluorimetric methods[11-15]. Few analytical methods were reported for determination of TEL and HCT in combination which includes HPLC, TLC[16-18]. However, no methods are reported for simultaneous estimation of TEL and HCT by simple spectroscopic methods in pharmaceutical preparations. Hence, the simultaneous spectroscopic method has been developed to estimate these two drugs from tablet dosage form[19.22]



Telmisartan

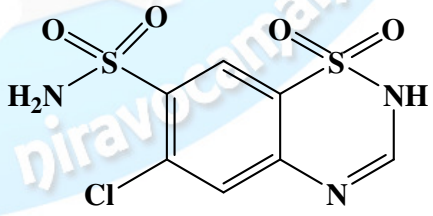


Fig. 2: Hydrochlorothiazide

Equipment

A double beam UV-visible spectrophotometer (Shimadzu, Japan) model UV-1700 with quartz cell 1 cm path length was used. Shimadzu balance (AUW-120D) was

used for all weighing.

Materials and Methods

Instrument used in current research was UV/ visible spectrophotometer with resolution of 1nm and 0.5 nm slit width (model UV-1700, Shimadzu). An electronic balance of (Shimadzu) 10 mg sensitivity and ultrasonicator (Modern Industrial Corporation) was used. Standard gift sample of TEL and HCT were supplied by Cipla and Aurochem Pharma Ltd. India respectively. TEL and HCT combination tablets (TELMIKIND^{R}- H, 40 mg TEL and 12.5 mg HCT, Mfg. by Mankind Pharmaceuticals, New Delhi, India) were purchased from the local pharmacy. 0.1 N Potassium Hydroxide (KOH) was used as a solvent and purchased from Merck Chemicals, India.

Method Development

Hence, these two wavelengths 295.5 and 273 nm were selected for estimation of TEL and HCT by simultaneous equation method.

Method-A

Simultaneous equation method.

For the selection of analytical wavelength for the Simultaneous Equation Method solutions of TEL (40 µg/ml) and HCTZ (12.5 µg/ml), were prepared separately by appropriate dilution of standard stock solution and scanned in the spectrum mode from 400 nm to 200 nm. From the overlain spectra of drugs, wavelengths 295.5 nm (λmax of TEL) and 273.0 nm (λmax of HCT) were selected for the simultaneous equations. The calibration curves for TEL and HCT were prepared in the concentration range of 10-90 µg/ml and 5-45 µg/ml respectively at both the wavelengths. The absorptivity values were determined for both the drugs at both the wavelengths. From the following set of equations the concentration of each component in the sample can be calculated, $Cx=(A_2ay_1-A_1ay_2)/(ax_2ay_1-ax_1ay_2)$, $Cy=(A_1ay_2-A_2ay_1)/(ax_1ay_2-ax_2ay_1)$, where

Cx= Concentration of TEL(40µg/mL)

Cy = Concentration of HCT(12.5µg/mL)

A_1 = Absorbance of sample solution at 295.5 nm

A_2= Absorbance of sample solution at 273 nm

ax_1 = Absorptivity value of TEL at 295.5 nm

ax_2 = Absorptivity value of TEL at 273 nm

ay_1 = Absorptivity value of HCT at 295.5 nm

ay_2 = Absorptivity value of HCT at 273 nm

Method-B

In the Absorption Ratio Method from the overlain spectra of both drugs, wavelengths 282.0 nm (iso-absorptive point), 295.5 nm (λmax of TEL) and 273.0 nm (λmax of HCT) were selected for the analysis. The calibration curves for TEL and HCT were plotted in the concentration range of 10-90 µg/ml and 5-45 µg/ml respectively at both the wavelengths respectively. The absorptivity values were determined for both the drugs at both the wavelengths. From the following set of equations the concentration of each component in the sample can be calculated, Cx = Qm-Qy/Qx- QyXA1 /a (1) and Cy = Qm-Qx/Qy-QxXA1 /a (2), where Cx is the concentration of TEL, Cy is the concentration of HCT, A1 is the absobance of sample at iso-absorptive wavelength 282.0 nm, 'a' is the mean absorptivity of TEL and HCT at iso-absorptive wavelength 282.0 nm, Qm is the ratio of absorbance of sample solution at 295.5 nm and at 282.0 nm, Qx is the ratio of absorptivities of TEL at 295.5 nm and at 282.0 nm and Qy is the ratio of absorptivities of HCT at 295.5 nm and at 282.0 nm.

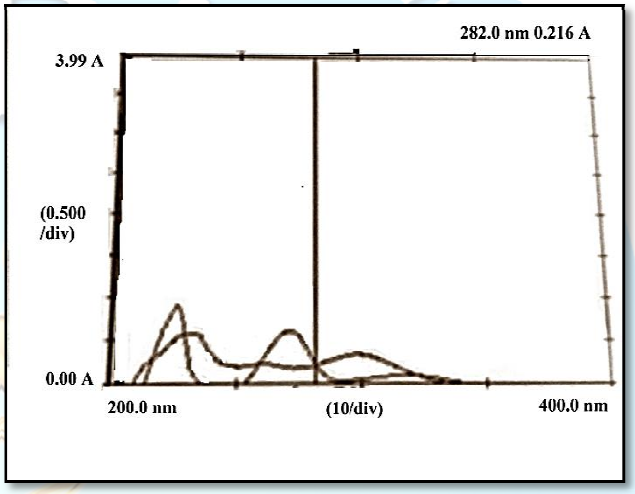


Fig.3: Iso Absorptive point of TEL & HCT

Preparation of standard solution

Standard stock solution of 100µg/ml each of TEL and HCT (10mg) were prepared in 0.1 N KOH. A dilution of stock solution was made with 0.1 N KOH. Standard stock solutions of TEL (100 µg/ml) and HCT (100 µg/ml) were prepared and used for the analysis.

Analysis of marketed formulation

Twenty tablets were weighed and finely powdered, an accurately weighed powder equivalent to one tablet containing 40.0 mg TEL and 12.5 mg of HCT was transferred to 100.0mL volumetric flask, 50.0mL 0.1 N KOH was added in it, ultrasonicated for 20 min., volume was made up to the mark with 0.1 N KOH. Diluted solution were filtered through Whatman filter paper no.42.The sample filtrate was further diluted (1.0mL of stock solution diluted to 10.0mL with0.1 N KOH) so as to get a final concentration of 40.0µg/mL of TEL and 12.5 µg/mL of HCT which was used for analysis. Absorbance of these solutions was measured at 295.5 nm and 273.0 nm of the both wavelength as A1 and A2 respectively. The procedure was repeated six times. The concentration of the two drugs in

the sample was determined, respectively. Amount of drug estimated in mg/tablet and percent label claim was calculated.

Method Validation

1. Calibration curve and linearity

The standard stock solutions containing 10 mg/ml each of TEL and HCT were further diluted to get linearity concentration 10-90 µg/ml for TEL and 5-45 µg/ml for HCT respectively. Each concentration was analyzed in triplicate. Calibration curve was plotted by taking absorbance on Y-axis and concentration on X-axis. The relation between drug and its absorbance is expressed by the equation y=mx+b, where 'm' is slope and 'b' is intercept.

2. Accuracy

Accuracy was established across the specified range of the analytical procedure.

3. Precision

Precision was ascertained by triplicate estimation of standard drugs on same day (intraday) and on three consecutive days (inter day). The %RSD reveals good precision (Table 2)

5. Limit of detection and limit of quantification

The limit of detection (LOD) and limit of quantification (LOQ) were estimated from the standard calibration curve. The residual standard deviation of regression line or standard deviation of y intercepts of regression lines was used to calculate LOD and LOQ. Here LOD=3.3X D/S and LOQ=10X D/S. Where D is the standard deviation of y intercept of regression line, S is the slope of calibration curve.

6. Robustness

To evaluate the robustness of the proposed method, small but deliberate variations in the optimized method parameters were done. The effect of change in wavelength on absorbance was studied. The tablet sample solution containing 40.0 µg/mL of TEL and 12.5 µg/mL of HCT was run into UV spectrophotometer under the varied conditions.The value for %RSD found to be < 2.0, which indicate excellent recoveries as revealed in Table 2.

Table No.1: Results of TEL and HCT estimation in Laboratory mixture and Tablet formulation

Sample		Simultaneous Equation Method		Q-Analysis method	
		TEL	HCT	TEL	HCT
Laboratory Mixture	%Mean*	99.42	99.40	99.65	99.53
	S. D.	0.8419	1.1333	0.8987	1.1295
	%R.S.D.	0.8519	1.1401	0.9018	1.1348
Tablet (TELMIKIND-H)	%Mean*	99.73	99.77	99.61	99.70
	S. D.	1.0789	0.8653	0.7759	1.3516
	%R.S.D.	1.0819	0.8673	0.7789	1.3556

Table 2. Summary of validation parameters

Parameters		Simultaneous Equation Method		Q-Analysis Method	
		TEL	HCT	TEL	HCT
Linearity range (µg/mL)		10-90 µg/ml	5-45 µg/ml	10-90 µg/ml	5-45 µg/ml
Accuracy % Mean* (%R.S.D.)	80%	99.25 % (0.857)	99.11 % (0.564)	99.13% (0.698)	99.07% (0.761)
	100%	99.46% (1.151)	99.42% (0.864)	99.32% (1.053)	99.18% (1.830)
	120%	99.54 % (0.973)	99.51 % (1.195)	99.25% (1.896)	99.23 % (1.787)
Precision (%R.S.D.)		1.0398	0.7634	1.1922	1.3558
Intra-day (n = 3)		1.3383	1.0793	1.2319	1.2011
Inter-day (n = 3)		0.4135	1.0764	1.3213	1.1763
LOD (µg/mL)		1.5502	0.4397	0.8745	0.6384
LOQ (µg/mL)		2.7744	1.3325	2.5796	1.9347
Robustness		Robust	Robust	Robust	Robust

Conclusion

The UV methods were validated as per ICH guidelines. The standard deviation and % relative standard deviations calculated for the proposed methods are low, indicating high degree of precision of the methods. The results of the recovery studies showed the high degree of accuracy of the proposed methods. Hence, it can be concluded that the developed methods are accurate, precise and selective and it can be employed successfully for the estimation of TEL and HCT in bulk and pharmaceutical dosage form. Thus this method can be used to differentiate the pure drugs of TEL and HCT from their marketed products.

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