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Validated Spectrophotometric Methods for Estimation of Telmisartan and Hydrochlorothiazide in Combined Tablet Dosage Form.

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Research Article

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Keywords: Telmisartan, Hydrochlorothiazide, simultaneous estimation, combined tablet dosage form.

ABSTRACT

Quantitative Spectrophotometric analysis of poorly water-soluble drugs involves use of various organic solvents, solubility enhancing agents, co solvents or Buffers. Major drawbacks of organic solvents include high cost, volatility and toxicity. On the other hand use of alkali or acids may reduce the stability of analytes throughout the process of estimation. In the present investigation, co-solvency technique has been employed to solubilize the poorly water-soluble drugs. Four perspicacious spectrophotometric methods for simultaneous estimation of Telmisartan (TEL) and Hydrochlorothiazide (HCTZ) in two component solid dosage forms have been developed. The methods employed Simultaneous Equation Method and Multicomponent mode of analysis at 295nm and 273nm (absorbance maxima of Telmisartan and Hydrochlorothiazide respectively), the Absorbance Ratio (Q-analysis) method at 283.0nm (iso-absorptive point) and 293.0nm (absorbance maxima of Telmisartan), the First Order Derivative Spectroscopy method at 273.0 nm for Telmisartan (zero cross for HCTZ) and 295.0 nm for Hydrochlorothiazide (zero cross for TEL). The methods utilized Methanol: Water (1:1) as a solvent and were found to be linear in the range of 4-24 µg/ml and 2-14 µg/ml for TEL and HCTZ respectively. The procedures were successfully applied for the simultaneous determination of both drugs in laboratory mixtures and in commercial tablet formulation.

INTRODUCTION

Telmisartan is chemically designated as 4'-[(1, 4'-dimethyl-2'-propyl [2,6'-bi-1H-benzimidazol]-1'-yl) methyl] [1,1'-biphenyl]-2-carboxylic acid [1]. It is an angiotensin II type I blocker and is used as an antihypertensive [2] along with Hydrochlorothiazide. It is a thiazide diuretic which reduces the reabsorption of electrolytes from the renal tubules, thereby increasing the excretion of sodium and chloride ions and consequently of water [3]. Chemically Hydrochlorothiazide is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7sulfonamide 1, 1-dioxide [1]. The combination of Hydrochlorothiazide and Telmisartan is useful in treatment of mild to moderate hypertension, and is well tolerated with a lower incidence of cough than ACE inhibitors. The marketed tablets contain Telmisartan and Hydrochlorothiazide in ratio of 40:12.5 [4]. The widespread use of these drugs in combination necessitates development of analytical methods for their simultaneous estimation. Several analytical procedures have been proposed for the quantitative estimation of Telmisartan and Hydrochlorothiazide separately and in combination with other drugs. Several spectrophotometric, Chemometric and Chromatographic [5-14] techniques have been reported using various Organic solvents, Alkalis, Acids and Buffers. After literature survey, it has been speculated to develop few simple rapid and accurate analytical methods of estimation by using co-solvency techniques, so as to reduce toxicity, cost, and ambiguity of annoying procedures.

MATERIALS AND METHODS

Materials

Standard gift sample of Telmisartan and Hydrochlorothiazide were provided by Lupin Ltd. Taluka Mulshi, Pune. Combined dose TEL and HCTZ tablets (Telista H - Telmisartan 40 mg + Hydrochlorothiazide 12.5 mg, Lupin Ltd.), were purchased from the local pharmacy.

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Instrumentation and standard Spectrophotometric conditions

A double-beam Shimadzu UV/Vis spectrophotometer, 1700 Pharmaspec, with spectral bandwidth of 2 nm, wavelength accuracy of ±0.5 nm and a pair of 1cm matched quartz cells, was used to measure absorbance of the resulting solution.

Preparation of Mixed Standard Stock Solution

Water: methanol (1:1) was prepared from analytical grade Methanol in double distilled water and used as solvent after assessing the solubility of drugs in different solvents. Standard stock solutions of TEL (100 µg/ml) and HCTZ (100 µg/ml) were prepared and used for the analysis.

Development of the Analytical Methods

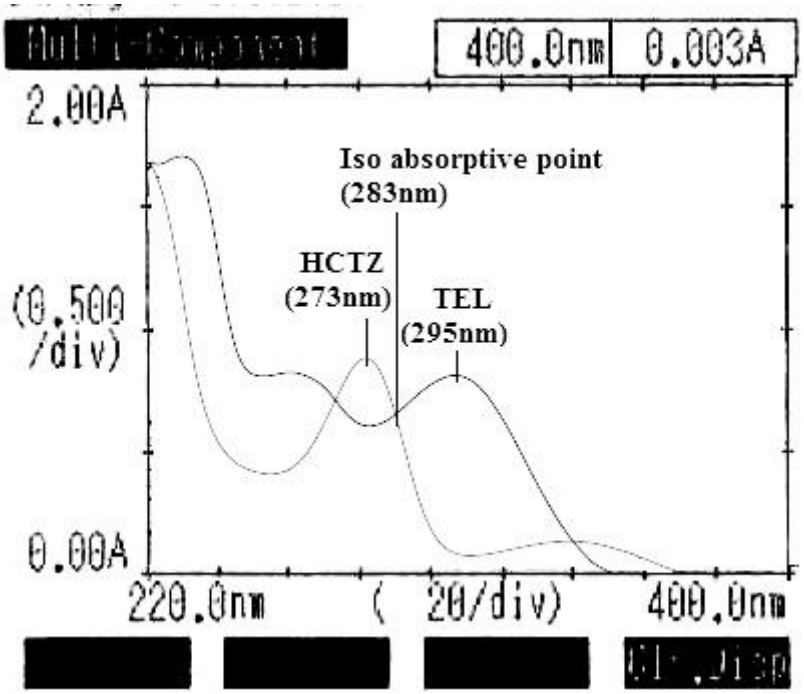

Figure 1: Overlain spectra of Telmisartan (TEL) and Hydrochlorothiazide (HCTZ).

Method-A

For the selection of analytical wavelength for the Simultaneous Equation Method [15] solutions of TEL (20 µg/ml) and HCTZ (6.5 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 [Fig. 1], wavelengths 295.0 nm (λ_{max} of TEL) and 273.0 nm (λ_{max} of HCTZ) were selected for the simultaneous equations. The calibration curves for TEL and HCTZ were prepared in the concentration range of 4-24 µg/ml and 2-14 µg/ml respectively at both the wavelengths respectively. The absorptivity values were determined for both the drugs at both the wavelengths and following equations were used, $A_1 = 553.2C_{TEL} + 141.2C_{HCTZ}$ (1) and $A_2 = 413.6C_{TEL} + 755.3C_{HCTZ}$ (2), where A_1 and A_2 are absorbances of the sample at 295.0 nm and 273.0 nm, respectively, 553.2 and 413.6 are absorptivities of TEL at 295.0 nm and 273.0 nm, respectively, 141.2 and 755.3 are the absorptivities of HCTZ at 295.0 nm and 273.0 nm, respectively. C_{TEL} is the concentration of TEL and C_{HCTZ} is the concentration of the HCTZ. The mixture concentration was determined by using the Eqns. 1 and 2.

Method-B

In the Absorption Ratio Method [15] from the overlain spectra of both drugs [Fig. 1], wavelengths 283.0 nm (iso-absorptive point) and 293.0 nm (λ_{max} of TEL) were selected for the analysis. The calibration curves for TEL and HCTZ were plotted in the concentration range of 4-24 µg/ml and 2-14 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, $Cx = Qm\text{-}Qy/Qx\text{-}QyXA_1 /a$ (1) and $Cy = Qm\text{-}Qx/Qy\text{-}QxXA_1 /a$ (2), where Cx is the concentration of TEL, Cy is the concentration of HCTZ, A_1 is the absobance of sample at iso-absorptive wavelength 283.0 nm, 'a' is the mean absorptivity of TEL and HCTZ at iso-absorptive wavelength 283.0 nm, Qm is the ratio of absorbance of sample solution at 295.0 nm and at

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283.0 nm, Qx is the ratio of absorptivities of TEL at 295.0 nm and at 283.0 nm and Qy is the ratio of absorptivities of HCTZ at 295.0 nm and at 283.0 nm.

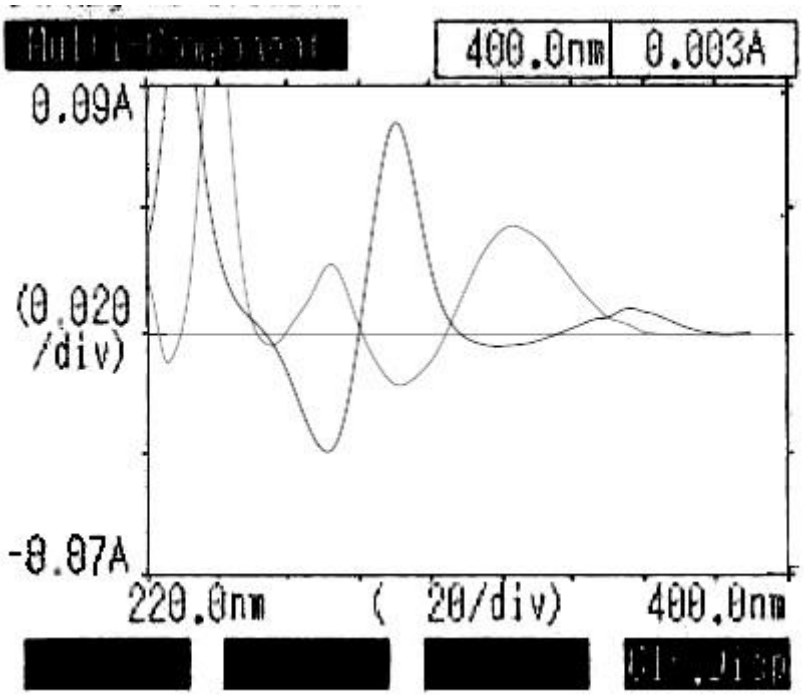

Figure 2: First Order Derivative spectra of Telmisartan (TEL) and Hydrochlorothiazide (HCTZ).

Method-C

In First Order Derivative Spectroscopy [15] [Fig. 2] solutions of TEL (20 µg/ml) and HCTZ (6.5 µg/ml), were prepared separately by appropriate dilution of standard stock solution and scanned in the spectrum mode from 400 nm to 200 nm. The absorption spectra thus obtained were derivatized from first to fourth Order. First Order derivative spectrum was selected for analysis of both drugs and wavelengths selected for quantitation were 273.0 nm for Telmisartan (zero cross for Hydrochlorothiazide) and 295.0 nm for Hydrochlorothiazide (zero cross for Telmisartan). The calibration curves for TEL and HTCZ were plotted in the concentration range of 4-24 µg/ml and 2-14 µg/ml respectively at both the wavelengths, respectively. The concentration of the individual drug present in the mixture was determined against the calibration curve in quantitation mode.

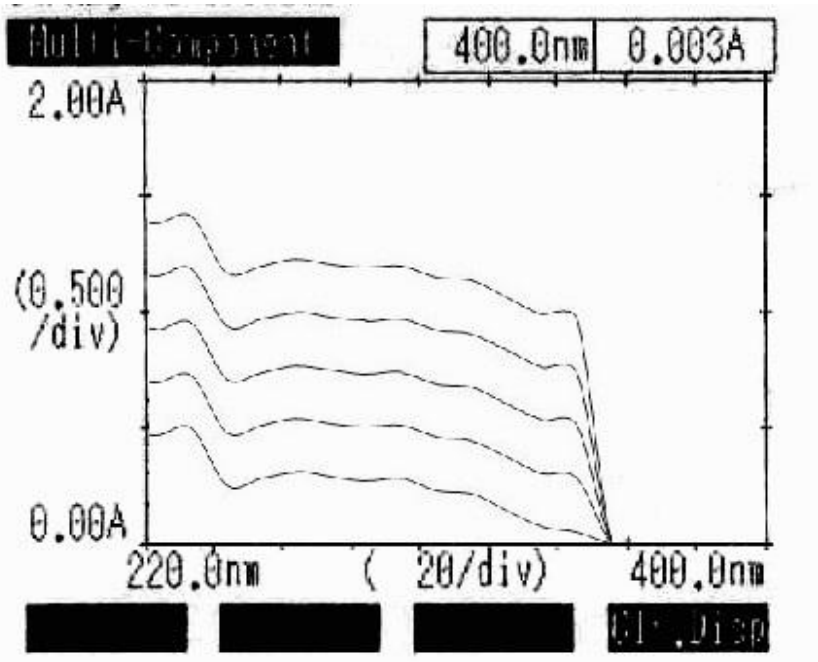

Figure 3: Overlain spectra of mixed standards of Telmisartan (TEL) and Hydrochlorothiazide (HCTZ).

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Method-D

In the Multi-Component Mode of analysis [16] [Fig. 3] five mixed standards of TEL and HCTZ in the ratio of 2:5 having concentrations in µg/mL of 6.4:2, 9.6:3, 12.8:4, 16:5 and 19.2:6 were prepared by appropriate dilution of the standard stock solutions and scanned in the region of 400 nm to 200 nm. Sampling wavelengths (295.0 nm and 273.0 nm) were selected on the trial and error basis. The concentration of individual drug was fed to the multi-component mode of the instrument. The instrument collects and compiles the spectral data from mixed standards and concentration of each component were obtained by spectral data of sample solution with reference to that of five mixed standards.

Analysis of marketed Formulation

For the estimation of drugs in the commercial formulations, twenty tablets were weighed and average weight was calculated. The tablets were crushed to obtain fine powder. Tablet powder equivalent to 100 mg of TEL was transferred to 100.0 ml volumetric flask containing 40 ml of Water: Methanol (1:1) and ultrasonicated for 5 min and diluted to the mark with Water: Methanol (1:1). The solution was then filtered through a Whatmann filter paper No. 41. From the filtrate suitable aliquots were completed to volume with methanol to get a concentration in the ratio of 3.2:1 taking into consideration its amount present in combined tablet formulation. The concentration of both TEL and HCTZ was determined by measuring the absorbance of the sample at 295.0 nm and 273.0 nm (Method-A), at 283.0 nm and 295.0 nm (Method-B), in the spectrum mode and values were substituted in the respective formulae to obtain concentrations. For (Method-C) concentration of both TEL and HCTZ was determined by measuring the absorbance of the sample at 273.0 nm and 295.0 nm in first order spectrum mode. For (Method-D) Sampling wavelengths (295.0 nm and 273.0 nm) were selected and five concentrations of marketed formulations were fed to the multi-component mode of the instrument. The results of the tablet analysis were calculated and presented in Table-1.

RESULTS AND DISCUSSION

Table 1: Results of Pharmaceutical analysis

Parameters	Method-A		Method-B		Method-C		Method-D	
	CEF	ORN	CEF	ORN	CEF	ORN	CEF	ORN
Lable Claim (mg/Tab)	200	500	200	500	200	500	200	500
Found (mg/Tab)	199.86	499.86	199.83	499.84	199.92	499.82	199.85	499.84
%Drug Content *	100.01	99.99	100.01	100.00	100.02	100.00	100.01	99.99
±S.D	0.06	0.028	0.066	0.030	0.059	0.030	0.074	0.033
%COV	0.059	0.028	0.066	0.030	0.059	0.030	0.074	0.033
SE	0.024	0.013	0.026	0.013	0.026	0.013	0.030	0.014

*Value for drug content (%) are the mean of five estimation, Method-A: Simultaneous Equation Method, Method-B: Absorbance Ratio , Method-C: First Order Derivative Spectroscopy Method-D: Multi-Component Mode of analysis, S.D: Standard Deviation, COV: Coefficient Of Variance and S.E: Standard Error.

Recovery studies

Recovery studies were carried out by standard addition method at three different levels 80%, 100% and 120%. The % recovery of TEL and HCTZ in the sample mixture was determined. The results of recovery studies obtained by proposed method were validated by statistical evaluation and are recorded in Table-2.

All four UV spectrophotometric methods were found to be simple, accurate, economic and rapid for simultaneous estimation of TEL and HCTZ in bulk and tablet dosage form. Solubility studies indicated that solubility of TEL and HCTZ in Water: Methanol (1:1) was excellent as compared to distilled water, buffer of pH 3.0, 0.1N NaOH, etc. Linearity range for TEL and HCTZ were found to be 4-24 µg/ml and 2-14 µg/ml respectively at respective selected wavelengths. The standard deviation, coefficient of variance and standard error were obtained for TEL and HCTZ as per required specification. The proposed methods were optimized and validated as per the ICH guidelines [17]. The methods discussed in the present work provide a convenient and accurate way for simultaneous analysis of TEL and HCTZ. Percent label claim for TEL and HCTZ in tablet, by all four methods, was found in the range of 99.99% to 100.02%. Standard deviation and coefficient of variance for six determinations of tablet sample, by all the methods, was found to be less than ±2.0 indicating the precision of all the methods. Accuracy of proposed methods was ascertained by recovery studies and the results are expressed as % recovery. Percent recovery for TEL and HCTZ, by all four methods, was found in the range of 99.95% to 100.087%, values of standard deviation and coefficient of variation were in the range of ±0.115 to ±0.519 and 0.083 to 0.226, respectively indicating the accuracy of proposed methods.

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A critical evaluation of the proposed methods was performed by statistical analysis of the experimental data. In order to demonstrate the validity and applicability of the proposed methods, recovery studies were performed by analyzing synthetic mixture of TEL and HCTZ with different composition ratio. Based on the results obtained, it is found that the proposed methods are accurate, precise, reproducible and economical and can be employed for routine quality control of Telmisartan and Hydrochlorothiazide in combined dose tablet formulation.

Table 2: Results of Recovery Studies

Method	Drug	Lable claim (mg/tab)	Amount (mg/ml)		%Recovery ± S.D	COV%
			Taken	Added		
Method-A	TEL	200	1	0.8	100.05±0.180	0.102
			1	1.0	99.95±0.146	0.179
			1	1.2	99.99±0.119	0.146
	HCTZ	500	1	0.8	100.09±0.119	0.119
			1	1.0	100.04±0.119	0.119
			1	1.2	100.01±0.089	0.119
Method-B	TEL	200	1	0.8	100.063±0.105	0.089
			1	1.0	100.01±0.13	0.104
			1	1.2	100.02±0.226	0.129
	HCTZ	500	1	0.8	100.043±0.120	0.226
			1	1.0	100.106±0.123	0.12
			1	1.2	99.976±0.090	0.123
Method-C	TEL	200	1	0.8	100.087±0.144	0.09
			1	1.0	100.016±0.083	0.144
			1	1.2	100.14±0.026	0.083
	HCTZ	500	1	0.8	100.026±0.120	0.026
			1	1.0	100.11±0.060	0.12
			1	1.2	100.053±0.198	0.06
Method-D	TEL	200	1	0.8	100.050±0.183	0.198
			1	1.0	100.036±0.181	0.183
			1	1.2	100.013±0.162	0.181
	HCTZ	500	1	0.8	100.03±0.519	0.162
			1	1.0	100.003±0.115	0.051
			1	1.2	100.05±0.180	0.115

%Recovery is mean of three estimation, Method-A: Simultaneous Equation Method, Method-B: Absorbance Ratio, Method-C: First Order Derivative Spectroscopy Method-D: Multi-Component Mode of analysis, S.D: Standard deviation and COV: Coefficient of Variance.

CONCLUSION

Thus, it may be concluded that the proposed methods of analysis are new, simple, cost-effective, environmentally friendly, safe, accurate and reproducible. Definitely, there is further scope of co-solvency technique for solubilizing poorly water soluble drugs. The proposed method can be successfully employed in the routine analysis of TEL and HCTZ containing dosage forms.

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