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Development and Validation of Analytical

Methods for Estimation of Valsartan and HCTZ

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Abstract

For the simultaneous measurement of valsartan and hydrochlorothiazide in a tablet dosage form, two UV-spectrophotometric techniques have been devised and validated. Using the absorbance measurements for valsartan and hydrochlorothiazide at two wavelengths (249.4 nm and 272.6 nm, respectively), the first technique included solving simultaneous equations. The Q-absorbance equation is formed at the isoabsorptive point of 258.4 nm and the hydrochlorothiazide peak of 272.6 nm in the absorbance ratio method, which was the second technique used. The results showed that, using 0.1 N NaOH as the solvent, the procedures were linear in the range of 5–30 µg/mL for valsartan and 4–24 µg/mL for hydrochlorothiazide. For valsartan and hydrochlorothiazide, respectively, at three different levels of standard adds, the mean percentage recovery was determined to be 100.20% and 100.19% for the simultaneous equation approach and 98.56% and 97.96% for the absorbance ratio method. The approaches' accuracy (intraday and interday) was confirmed to be within bounds. The present investigation's results suggest that two methods for simultaneously estimating valsartan and hydrochlorothiazide in tablet dosage form are straightforward, quick, accurate, precise, and cost-effective. These methods can be successfully applied to routine laboratory analyses and quality control pharmaceutical formulations.

KEYWORDS:-Valsartan, Hydrochlorothiazide, Absorbance ratio, Standard solution, Simultaneous

1. Introduction

VAL (Figure 1) is a nonpeptide that has the form of N-(1-oxopentyl)-N-[[2′-(1H-tetrazol-5-yl) [1,1′-biphenyl]-4-yl] methyl]-L-valine [1]. It is an effective, very selective, oral, active, and specific angiotensin II receptor antagonist that is used to treat hypotension. Hydrochlorothiazide (HCT) is a diuretic medication that is 6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulphonamide,1,1-dioxide (Figure 2) [2]. First-line treatment including a fixed-dose combination of valsartan and hydrochlorothiazide results in BP normalisation with a high response rate in individuals with mild hypertension. This medication combination is justified by the fact that oral valsartan plus hydrochlorothiazide administration has been shown to be more successful than either drug alone in the treatment of hypertension in individuals whose blood pressure is not sufficiently controlled by monotherapy [3,4]. There are very few methods available in the literature for determining the dose of hydrochlorothiazide and valsartan in tablets. The analytes were separated on a Zorbax SB-Aq C18 column using acetonitrile −10 mM ammonium acetate (60:40, v/v, pH 4.5) as mobile phase in a liquid chromatography/tandem mass spectrometry technique that involves protein precipitation [5]. The formulation of tablets and the creation of a validated stability indicating HPLC method [6] and the HPLC method for the simultaneous detection of hydrochlorothiazide, amlodipine, and valsartan in dosage form and spiked human plasma [7] were mentioned in another piece of literature. Ion pair chromatography [10] and HPTLC [8, 9] can be used in various ways to estimate both medications simultaneously. Additionally, certain UV spectroscopic approaches are discussed, whereby the first derivative method, AUC method, and simultaneous method were devised. [11–16].

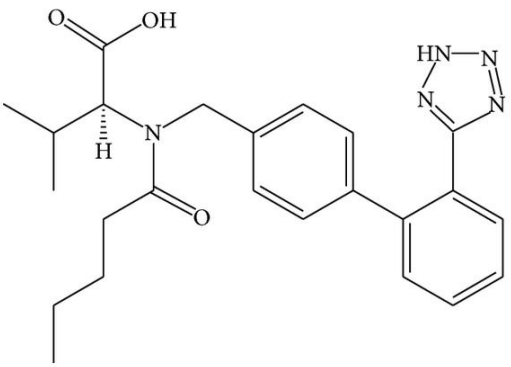

Fig. 1: Structure of VAL

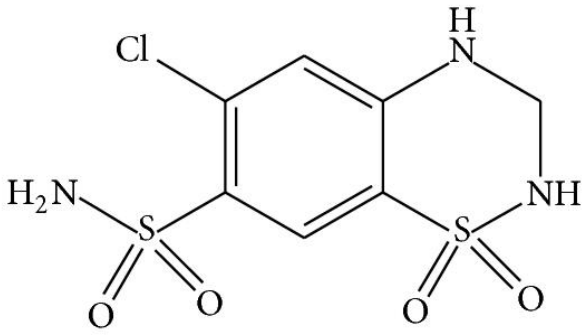

Fig. 2: Structure of HCTZ

Drug combination estimation carried out simultaneously is often accomplished by separation by chromatographic techniques such as HPLC, GC, HPTLC, and so on. These techniques are very reproducible, accurate, and exact, but they come at a high cost for analysis since they require expensive equipment, reagents, and training. Therefore, it makes sense to provide a more straightforward and affordable approach for drug estimate in tandem with routine formulation analysis. When it comes to simultaneously estimating the medication combination with an efficacy comparable to chromatographic approaches, spectrophotometric analysis meets this condition [17]. One other

benefit of the suggested techniques is the 0.1 N sodium hydroxide solvent, which is far less expensive than methanol.

Establishing such a technique and using it to analyse the drug content of tablets was the aim of this research, which was also validated in compliance with standards for good laboratory practice and the International Conference on Harmonisation (ICH) [18]. This study presents two spectrophotometric techniques for valsartan quantification using hydrochlorothiazide and the absorbance ratio approach. (method 2).

2. Materials and Methods

2.1. Instrument

A double-beam Shimadzu UV-Visible spectrophotometer, with spectral bandwidth of 1 nm, wavelength accuracy nm, Software- UV-Probe, and a pair of 1 cm matched quartz cells, was used to measure absorbance of the resulting solution.

2.2. Materials

The marketed preparation VALENT-H containing Valsartan 80 mg, Hydrochlorothiazide 12.5 mg manufactured by Lupin Pharmaceuticals Pvt Ltd., India, was used for analysis. Sodium hydroxide was procured, which was used as a solvent for both methods.

2.3. Selection of an Appropriate Solvent System

A variety of solvent systems, including methanol, distilled water, 0.1 N NaOH, and NHCl, were tested in an effort to find a suitable solvent that would be stable and suitable. Since both medications were soluble in 0.1 N NaOH, this solvent solution was chosen to determine the concentrations of valsartan and hydrochlorothiazide.

2.4. Preparation of Stock Standard Solutions

The preparation of a stock standard solution containing 1000 µg/mL of valsartan involved dissolving 10 mg of the drug in 10 mL of 0.1 N NaOH in a 10 mL volumetric flask while vigorously shaking it. A working solution of 100 µg/mL was obtained by extracting 1 mL from the stock standard solution and diluting it with solvent to make 10 mL. Similarly, 10 mg of hydrochlorothiazide was dissolved in 10 mL of 0.1 N NaOH in a 10 mL volumetric flask with vigorous shaking to create the stock standard solution of 1000 µg/mL. A workable solution containing 100 µg/mL was obtained by further diluting this solution.

2.5. Selection of Analytical Wavelengths

The analytical wavelengths were selected by independently scanning the working solutions of each medicines between 400 nm and 200 nm. Both medications' overlay spectra were captured (Figure 3). Using the simultaneous

equation approach, wavelengths 249.4 nm (of VAL) and 272.6 nm (of HCT) were chosen from overlay spectra for investigation of both medications. Additionally, using the absorbance ratio approach, the wavelengths of 272.6 nm (of HCT oth medicines.

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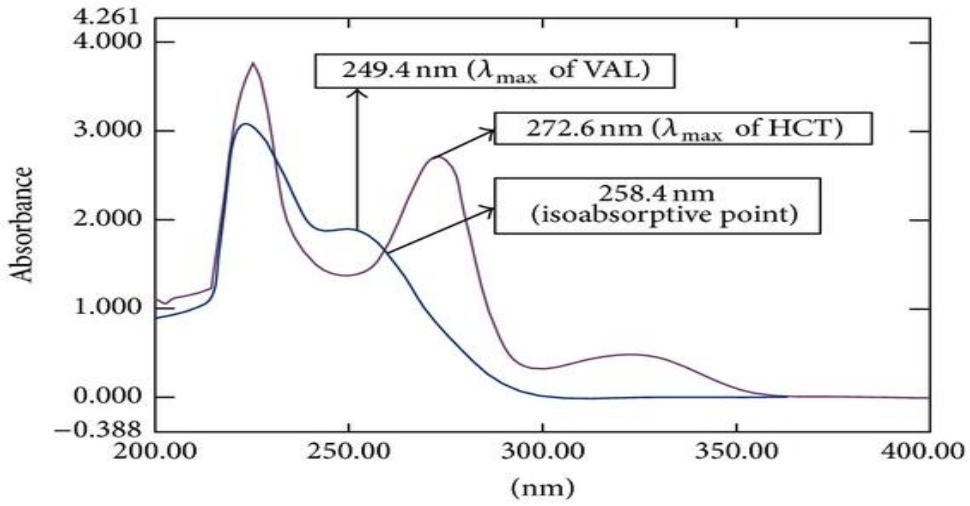

Fig. 3: Overlay spectra of VAL and HCTZ

2.6. Linearity Study

For VAL and HCT, the concentration ranges where the linear absorbances were achieved were 5–30 µg/mL and 4–24 µg/mL, respectively. For technique 1, the absorbances of these solutions were measured at 249.4 nm and 272.6 nm, and for method 2, at 258.4 nm and 272.6 nm. Absorbance versus concentration was plotted to create the calibration curve. However, for VAL and HCT, the pill ratio was 80:12.5, or 6.4:1. In order to create the technique, the tablet ratio for both procedures determined the concentration ranges: 12.8–76.8 µg/mL for VAL and 2–12 µg/mL for HCT.

2.8. Application of Proposed Methods for Standard Mixture

By weighing 80 mg of VAL and 12.5 mg of HCT in a 10 mL volumetric flask, a standard combination of VAL and HCT was created. To the volumetric flask, 5 mL of 0.1 N NaOH was added, and both medications were entirely dissolved. To get the concentration of 8000 µg/mL of VAL and 1250 µg/mL of HCT, the volume was finally adjusted to the mark using 0.1 N NaOH. After transferring the appropriate volume of 0.1 mL to a 10-mL volumetric flask, the solvent was diluted up to the mark to obtain 80 and 12.5 µg/mL of VAL and HCT, respectively. The solutions were scanned within the 400–200 nm range, and the absorbances of the sample solutions were noted at 249.4 nm and 272.6 nm. that is, and, respectively, for method 1. The concentrations of the two drugs in sample solution (and) were determined, by using (3). For method 2, absorbances of the sample solutions were recorded at 258.4 nm and 272.6 nm, that is, and, respectively. The concentrations of the two drugs in sample solution (and) were determined, by using (5). Results are shown in Table 1.

Table 1: Application of proposed method for standard mixture.

Name of drug	Amount taken (mg)	% Amount found (n= 6)		% RSD	
		Method 1	Method 2	Method 1	Method 2
VAL	80	100.84	99.68	0.29	0.96
HCT	12.5	101.42	100.88	0.30	0.42

2.9. Application of Proposed Method for Analysis of Tablets

Twenty pills were ground into a fine powder, weighed, and the average weight was calculated. The powder sample, which weighed 80 mg of VAL and 12.5 mg of HCT, was put into a 10-milliliter volumetric flask filled with 0.1 N NaOH and sonicated for 20 minutes. The volume was then marked with the same solvent and filtered using Whatmann filter paper number 41. To obtain a concentration of 12.5 µg/mL of HCT and 80 µg/mL of VAL, the resultant solution was further diluted. Absorbance of sample solution at chosen wavelengths was measured against blank using a 400–200 nm scan of the prepared solution. In procedure 1, the two medicines' concentrations in sample solutions (and) were calculated using (3). The results of the same are reported in Table 2.

Table 2: Application of proposed method for analysis of tablets.

Tablet sample	Label claim (mg/tab)	% Label claim (n = 6)		% RSD	
		Method 1	Method 2	Method 1	Method 2
VAL	80	98.75	98.29	1.20	0.54
HCT	12.5	101.50	99.12	0.29	0.68

3. Validation of Proposed Methods

The method was validated in terms of linearity, accuracy, precision, specificity LOD, LOQ, ruggedness, and robustness.

3.1. Accuracy

Accuracy of the method was assessed by percentage recovery experiments performed at three different levels, that is, 80, 100, and 120%. Known amounts of standard VAL and HCT solutions were added to the preanalyzed sample solutions; absorbances were recorded and reanalyzed by proposed method. The % recovery was calculated by usingwhere = total amount of drug estimated, = amount of drug found on preanalyzed basis, and = amount of bulk drug added.

Results of recovery studies are shown in Table 3.

Table 3: Results of recovery studies.

Recovery level	Initial amount (μg/mL)		Concentration of std		% Recovery (n= 3)			
					Method 1		Method 2	
	VAL	HCT	VAL	HCT	VAL	HCT	VAL	HCT
80%	20	2.5	16	1.6	98.89	100.55	99.51	99.63
100%	20	2.5	20	2.0	100.98	99.83	100.8	99.76
120%	20	2.5	24	2.4	100.73	100.19	101.0	100.3
		Mean			**100.20**	**100.19**	**100.40**	**100.20**

3.2. Precision

Precision is the measure of how close the data values are to each other for a number of measurements under the same analytical conditions.

3.2.1. Intraday and Interday Precision

By examining three separate VAL and HCT solutions on the same day and three distinct days over the course of a week, intraday and interday fluctuations were ascertained.

The analysis of 38.4 μg/mL, 51.2 μg/mL, and 64 μg/mL for VAL and 6 μg/mL, 8 μg/mL, and 10 μg/mL HCT performed three times in the same day were used to assess the intraday precision.

By examining the aforementioned medication concentrations for three separate days over the course of a week, interday precision was ascertained. The results are shown in Table 4.

Table 4: Results of intraday and interday precision.

Drug	Amount taken (μg/mL)	Intra-day (n = 3) % RSD		Inter-day (n = 3) % RSD	
		Method 1	Method 2	Method 1	Method 2
VAL	38.4	0.368	1.589	1.122	1.055
	51.2	0.358	0.760	0.879	0.908
	64	0.276	1.076	0.793	0.799
	Mean	0.334	1.143	1.143	0.920
HCT	6	1.439	1.085	1.722	1.376
	8	1.674	1.059	1.227	1.360
	10	0.970	0.987	1.256	0.895
	Mean	1.361	1.044	1.044	1.210

3.3. Specificity

It was assessed how other excipients could interfere. Using the same experimental and environmental settings, 10µg/mL of microcrystalline cellulose and starch were added individually to standard solutions 64µg/mL of VAL and 10µg/mL of HCT.

3.4. Ruggedness

The method's robustness was demonstrated by the analysis of two separate analysts' standard solutions, 64 µg/mL of VAL and 10 µg/mL of HCT, under identical experimental and environmental circumstances.

3.5. Robustness

The method's robustness was demonstrated by the analysis of standard solutions, which included 64 µg/mL of VAL and 10 µg/mL of HCT, using two distinct solvents under identical experimental and environmental circumstances.

4. Results and Discussions

Using the absorbance ratio approach, an analytical method has been devised for the simultaneous measurement of VAL and HCT in combination pharmaceutical dose form. The absorbance ratio technique was used to pick wavelengths of 258.4 nm (isoabsorptivity point) and 272.6 nm (HCT) in 0.1 N NaOH for the examination of both medicines. For VAL, linearity was seen in the range of 5–30 µg/mL() and for HCT, 2–16 µg/mL (). When the suggested approach was used for pharmaceutical formulation, it was discovered that the percentage label claims for VAL and HCT were, respectively, 98.29 and 99.12. The amount of medication assessed using the suggested approach agreed well with the claim on the label. The recovery experiments examined the method's accuracy at three distinct levels: 80%, 100%, and 120%. It was discovered that the mean percentage recovery for VAL and HCT was 100.40 and 100.20, respectively. The interday and intraday study, which demonstrates that the method's percentage R.S.D. is less than 2, demonstrated the method's precision. The lack of a statistically significant difference across operators in the findings suggests that the suggested procedure was robust. Furthermore, no statistically significant variation was seen between the solvent strengths, indicating the robustness of the approach. Determining LOD and LOQ allowed for the assessment of the method's sensitivity. The results for VAL showed that the LOD and LOQ were 1.60 and 4.86 µg/mL, respectively. The LOD and LOQ for HCT were determined to be 0.32 and 0.97 µg/mL, respectively. The summary of validation parameters is presented in Table 5.

Table 5: Summary of validation parameters.

Methods	Method 1		Method 2	
	VAL	HCT	VAL	HCT
λ_{max}	249.4 nm	272.6 nm	258.4 nm	272.6 nm
Linearity range (μg/mL)	12.8–76.8	2–12	12.8–76.8	2–12
Regression equation	$Y = 0.150x + 0.081$	$Y = 0.181x + 0.079$	$Y = 0.0269X + 0.064$	$Y = 0.0542X + 0.013$
Slope (m)	0.150	0.181	0.0269	0.0542
Y – intercept (c)	0.081	0.079	0.064	0.013
Correlation coefficient (r^2)	0.998	0.998	0.999	0.999
% recovery ($n = 3$)	100.20	100.19	100.40	100.20
LOD (μg/mL)	1.60	0.37	1.60	0.32
LOQ (μg/mL)	4.87	1.12	4.86	0.97
Molar absorptivity (lit/mole/cm)	14894.78	16613.89	12242.19	16643.66
Sandell's sensitivity (μg/sqcm/0.001)	0.02924	0.01793	0.03558	0.01789
Standard error	1.196 × 10−3	2.468 × 10−3	0.8381×10^{-3}	2.8324×10^{-3}
Precision (% RSD)				
Intra- day ($n = 3$)	0.334	1.361	1.143	1.044
Inter-day ($n = 3$)	0.931	1.402	0.920	1.210
Specificity (% RSD)				
Addition of MCC	1.6	1.8	0.9	1.2
Addition of starch	0.5	0.8	0.3	0.7
Ruggedness (% RSD)				
Analyst I ($n = 3$)	0.5	0.6	0.2	0.5
Analyst II ($n = 3$)	1.2	1.1	1.1	0.9
Robustness (% RSD)				
0.2 N NaOH ($n = 3$)	0.8	1.2	1.6	1.5
0.5 N NaOH ($n = 3$)	0.5	1.3	0.8	1.2

5. Conclusion

The proposed spectrophotometric methods were found to be simple, sensitive, accurate, precise, reproducible, specific, robust, and economical and can be used for the routine simultaneous estimation of VAL and HCT in pharmaceutical formulations.

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