DEVELOPMENT AND VALIDATION OF SPECTROPHOTOMETRIC METHOD FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN, CHLORTHALIDONE AND METOPROLOL SUCCINATE FROM THE COMBINED DOSAGE FORM

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Abstract

Telmisartan, chlorthalidone, and metoprolol succinate in pharmaceutical dosage form have all been simultaneously estimated using a straightforward, specific, accurate, and exact UV spectrophotometric technique. The methodology relied on measuring absorbance at each absorbance maximas 254 nm, 275 nm and 224 nm, of Telmisartan, Chlorthalidone and Metoprolol succinate in Methanol Correspondingly. Calibration curve of Telmisartan, Chlorthalidone and Metoprolol succinate were found to be linear in the concentration ranges of 3-15 µg/ml, 0.5-2.5 µg/ml and 2-10 µg/ml respectively. LOD and LOQ were 0.5 µg/ml and 1.6 µg/ml for Telmisartan, 0.09 µg/ml and 0.27 µg/ml for Chlorthalidone and 0.3 µg/ml and 1.02 µg/ml for Metoprolol succinate. The method were validated following ICH guidelines. The stated method could be used as a simple strategy for the quality control of the medications under study, based on the proposed results.

Keywords: Telmisartan; Chlorthalidone; Metoprolol succinate; Simultaneous equation method; Validation.

Introduction

Telmisartan is a 2-(4-{[4-Methyl-6-(1-methyl-1H-1,3-benzodiazol-2-yl)-2-propyl-1H-1,3benzodiazol-1-yl]methyl}phenyl)benzoic acid (Fig-1), an angiotensin II receptor blocker with high affinity for the angiotensin II receptor type 1 (AT1). It functions by obstructing an internal chemical that tightens blood arteries. Telmisartan causes the blood vessels to relax as a result. Its molecular weight is 514.62 g/ml and its formula is C33H30N4O2 [1,2]. Chlorthalidone, a drug used in the treatment and control of hypertension, is a (RS)-2-Chloro-5-(1-hydroxy-3-oxo-2,3-dihydro-1H-isoindol-1-yl)benzene-1-sulfonamide (Fig-2). This medication belongs to the class of thiazide-like diuretics. By blocking the Na/Cl symporter, it prevents chloride from being absorbed at the distal convoluted tubule level and hence sodium reabsorption. This eliminates sodium reabsorption, which keeps the sodium concentration of the nephron's distal convoluted tubule higher. Its chemical formula is C14H11ClN2O4S, and its molecular weight is 338.77 g/ml [3,4]. Metoprolol succinate is a (RS)-1-[4-(2-Methoxyethyl)phenoxy](propan-2-yl)amino] -3-Propan-2-ol, an extended-release tablet (Fig-3), is recommended for the long-term treatment of pectoris angina. Patients with ischemic, hypertensive, or cardiomyopathic heart failure who are symptomatic and stable should receive treatment (NYHA Class II or III). It weighs 652.8 g/ml and has the chemical formula C34H56N2O10 [5,6].

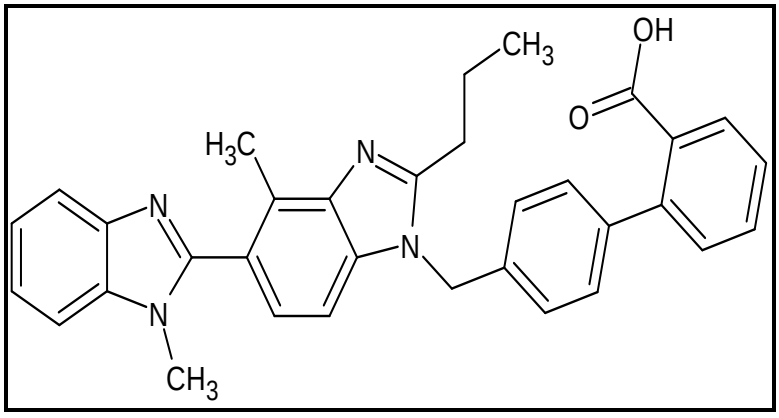

Figure-1: Chemical Structure of Telmisartan

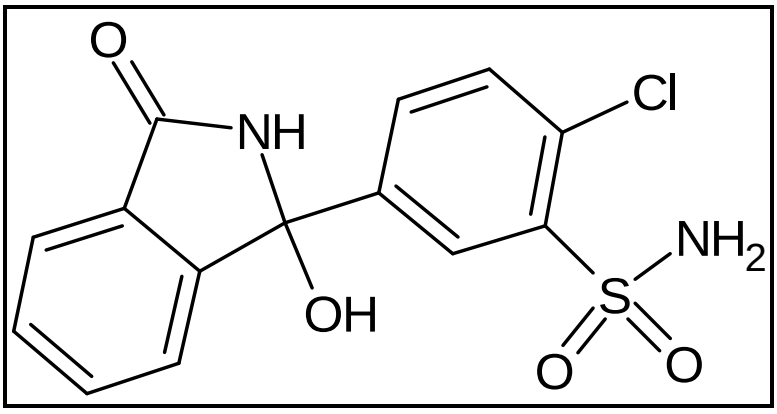

Figure-2: Chemical Structure of Chlorthalidone

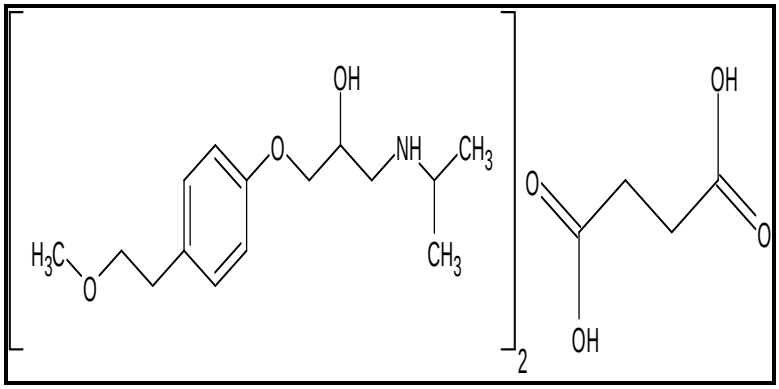

Figure-3: Chemical Structure of Metoprolol succinate

The simultaneous equation method in ultraviolet and visible spectrophotometry is widely utilized in the pharmaceutical industry. Technique is predicated on the fundamental principle that the absorbances at three specific wavelengths can be expressed as a system of simultaneous equations. The simultaneous equation method directly incorporates the concentrations of the individual components and their respective molar absorptivities.

By considering the absorbances at three chosen wavelengths, a system of equations is formulated, where each equation corresponds to one wavelength. These equations involve the concentrations of the components as variables and the coefficients are the molar absorptivities of each component at the respective wavelengths. Through the simultaneous solution of these equations, the concentrations of the components can be accurately determined, providing a robust and precise analytical approach.

A review of the literature revealed a number of techniques for the examination of individual medications and drug combinations, including UV [1,3,5,7,8], RP-HPLC [9,10,11], RP-LC/MS [12], and HPTLC [13,14]. However, no methods for the simultaneous equation method of concurrent determination for Telmisartan, Chlorthalidone and Metoprolol succinate was published. Thus, the current study set out to create and evaluate the spectrophotometric method using simultaneous equations for simultaneously estimating telmisartan, chlorthalidone, and metoprolol succinate.

MATERIALS AND METHODS

Instrument

Using a Shimadzu model UV-1650PC double beam UV/visible double beam spectrophotometer with a 1 nm spectral bandwidth and 1 cm thickness quartz cell, as well as a calibrated analytical balance (Shimadzu ELB-300), UV experiments were conducted.

Materials

Receiving a free sample of the bulk medications Telmisartan, Chlorthalidone, and Metoprolol succinate from Synthiya Research Labs Private Limited, Puducherry Telmisartan 40 mg, Chlorthalidone 6.25 mg and Metoprolol succinate 25 mg ER Tablets, which make up the CTD®-MT 6.25/25/40 formulation, were bought at a nearby pharmacy. Methanol was purchased from Sisco Research Laboratories pvt.Ltd, Mumbai.

SIMULTANEOUS EQUATION METHOD

If a sample contains three absorbing drugs, each of which absorbs at the λmax of the other, it may be possible to determine both drugs simultaneously using multi component analysis UV Spectrophotometric "Simultaneous Equation Method".

Three wavelengths selected for the development of the simultaneous equations are 254 nm, 275 nm and 224 nm. The absorptivity values determined for Telmisartan are 0.205 (ax1), 0.098 (ax2), 0.073 (ax3) and for Chlorthalidone are 0.244 (ay1), 0.028 (ay2), 0.02 (ay3) and for Metoprolol succinate are 0.0855 (az1), 0.007 (az2), 0.0195 (az3) at 224 nm, 254 nm and 275 nm respectively. These values are means of six estimations. The absorbance and absorptivity at these wavelengths were substituted in equation 1, 2 and 3 to obtain the concentration of both drugs.

$$\mathrm{Cx} = \frac{\mathrm{A1(ay2az3 - az2ay3) - ay1(A2az3 - az2A3) + az1(A2ay3 - ay2A3)}}{\mathrm{ax1(ay2az3 - az2ay3) - ay1(ax2az3 - az2ax3) + az1(ax2ay3 - ay2ax3)}} \ldots\ldots 1$$

$$\mathrm{Cy} = \frac{\mathrm{ax1(A2az3 - az2A3) - A1(ax2az3 - az2ax3) + az1(ax2A3 - A2ax3)}}{\mathrm{ax1(ay2az3 - az2ay3) - ay1(ax2az3 - az2ax3) + az1(ax2ay3 - ay2ax3)}} \ldots\ldots 2$$

$$\mathrm{Cz} = \frac{ax1(ay2A3 - A2ay3) - ay1(ax2A3 - A2ax3) + A1(ax2ay3 - ay2ax3)}{\mathrm{ax1(ay2az3 - az2ay3) - ay1(ax2az3 - az2ax3) + az1(ax2ay3 - ay2ax3)}} \ldots\ldots 3$$

Cx, Cy and Cz are the concentration X, Y and Z.
ax1, ax2 and ax3 are the absorptivities of X.
ay1, ay2 and ay3 are the absorptivities of Y.
az1, az2 and az3 are the absorptivities of Z.

Where Cx, Cy and Cz are concentration of Telmisartan, Chlorthalidone and Metoprolol succinate respectively in µg/ml. 0.792(A1), 0.319(A2) and 0.247(A3) are the absorbance of the mixture at 224 nm, 254 nm and 275 nm respectively.

PREPARATION OF STANDARD SOLUTION

The Stock solution of 100 µg/ml of Telmisartan, Chlorthalidone and Metoprolol succinate were prepared in methanol. A solution of Telmisartan (9 µg/ml), Chlorthalidone (1.5 µg/ml) and Metoprolol succinate (6 µg/ml) and mixture of Telmisartan, Chlorthalidone and Metoprolol succinate (16.5 µg/ml) each were prepared in methanol. The solutions were scanned in UV region. From the overlain spectra, wavelength 254 nm, 275 nm and 224 nm were selected. The different concentration of Telmisartan (3-15 µg/ml), Chlorthalidone (0.5-2.5 µg/ml) and Metoprolol succinate (2-10 µg/ml) were prepared from respective stock solution and scanned in UV region. The Linearity range of Telmisartan, Chlorthalidone and Metoprolol succinate obeyed Beer -Lambert's law condition.

METHODOLOGY

In the wavelength range of 200–400 nm, the absorption spectra of these dilutions were monitored and recorded against methanol as a blank. The absorbance was noted at selected wavelength of 254 nm, 275 nm and 224 nm for Telmisartan, Chlorthalidone and Metoprolol succinate respectively. UV spectrum of Telmisartan at 254 nm with concentration of 9 µg/ml is shown in (fig-4). UV spectrum of Chlorthalidone at 275 nm with concentration of 1.5 µg/ml is shown in (fig-5). UV spectrum of Metoprolol succinate at 224 nm with concentration of 6 µg/ml is shown in (fig-6). Five samples were made by transferring aliquots of different concentrations from Telmisartan, Chlorthalidone and Metoprolol succinate standard solutions into a set of 10-mL volumetric flasks and diluting to volume with methanol. The samples were analyzed using the procedures outlined under the linearity and calibration graphs for each method, and the concentrations of each drug were calculated. UV spectrum of mixture is shown in (fig-7). Contents of 10 CTD®-MT 6.25/25/40 tablets (40 mg Telmisartan, 6.25 mg Chlorthalidone and 25 mg Metoprolol succinate per tablet) were weighed and mixed well. A weighed powder equivalent to one tablet was accurately transferred to 10-mL volumetric flask with methanol, shaken vigorously for 20 min, filtered and adjusted to 10 mL with methanol. Further dilution with methanol was made to prepare five samples of different concentrations. The samples were analyzed following the procedure mentioned for each method under the linearity and calibration graphs and the concentration of each drug was computed. UV spectrum of formulation is shown in (fig-8). The five concentration of Telmisartan, Chlorthalidone and Metoprolol succinate, UV-spectrum were shown in (fig-9, 10, 11).

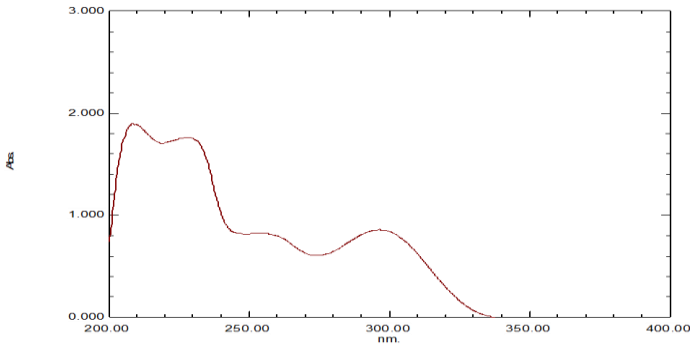

Figure-4: UV spectrum of Telmisartan at 254 nm (9 µg/ml)

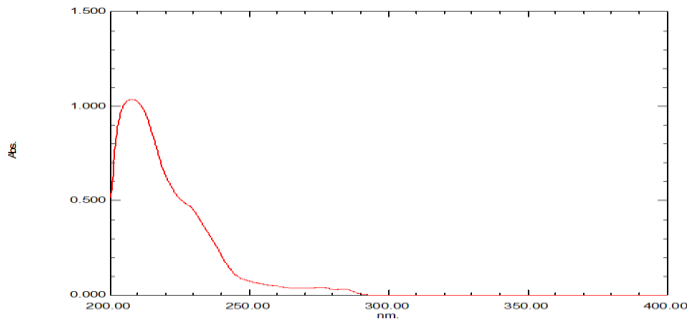

Figure-5: UV spectrum of Chlorthalidone at 275 nm (1.5 µg/ml)

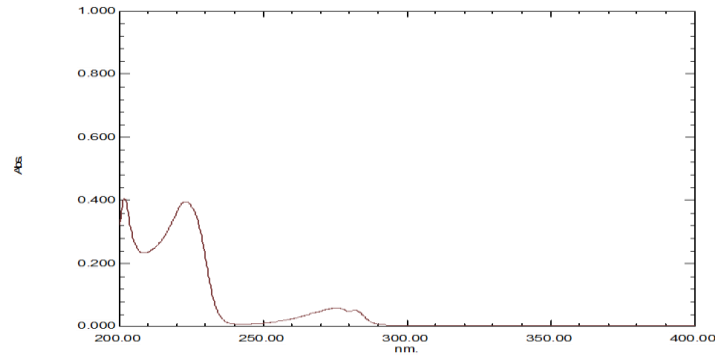

Figure-6: UV spectrum of Metoprolol succinate at 224 nm (6 µg/ml)

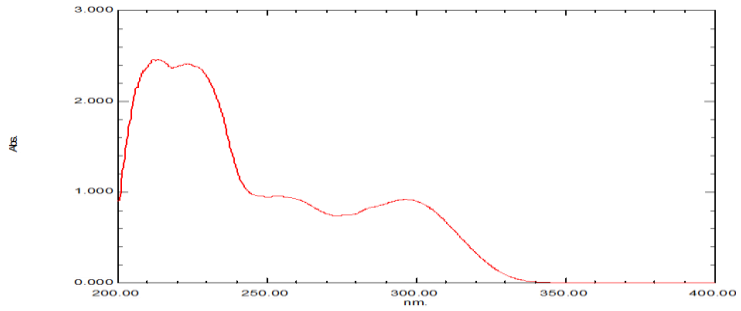

Figure-7: Mixture of Telmisartan, Chlorthalidone and Metoprolol succinate

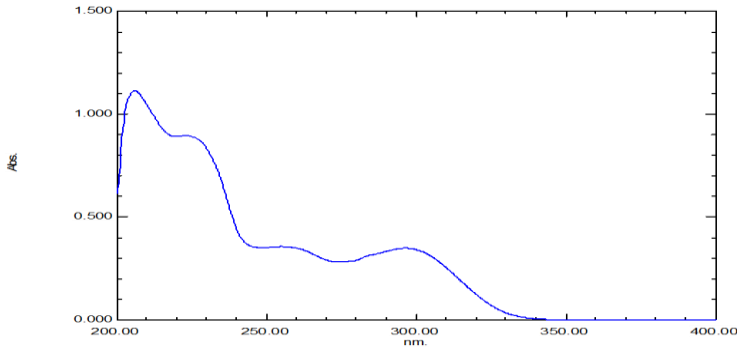

Figure-8: Formulation of Telmisartan, Chlorthalidone and Metoprolol succinate

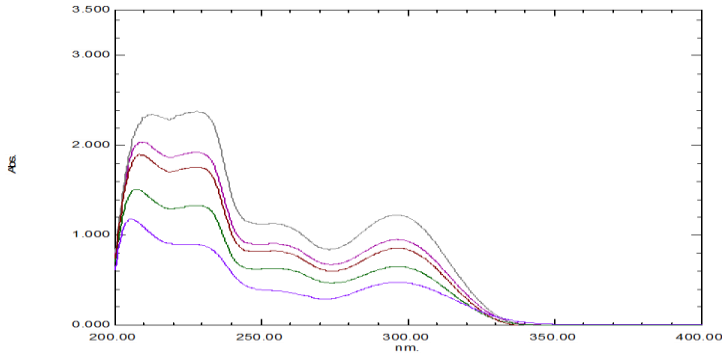

Figure-9: UV spectrum of Telmisartan at 254 nm (3-15 µg/ml)

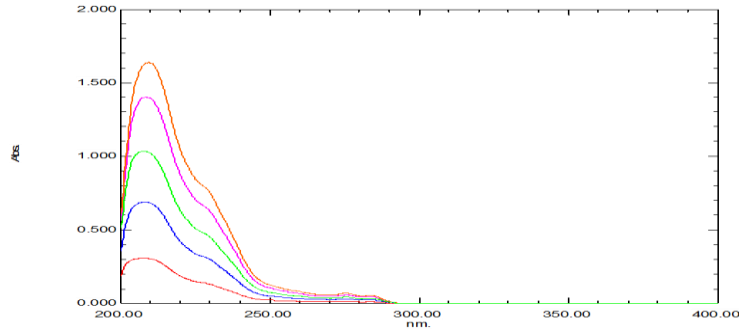

Figure-10: UV spectrum of Chlorthalidone at 275 nm (0.5-2.5 µg/ml)

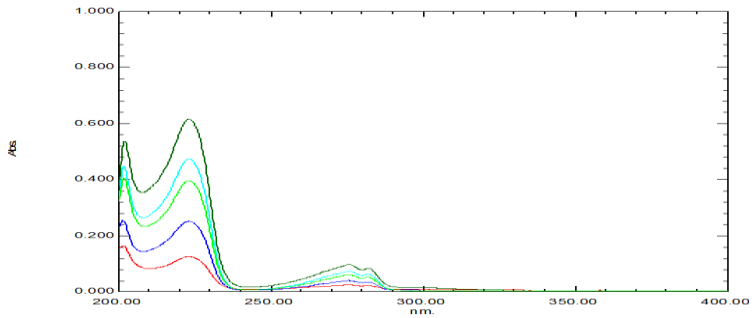

Figure-11: UV spectrum of Metoprolol succinate at 224 nm (2-10 µg/ml)

METHOD VALIDATION

Linearity

ICH states that, the analytical ability of method to yield test findings that are exactly reasonable in relation to the analyte concentration in the sample within a specified range is known as linearity. By measuring and comparing the concentrations of Telmisartan, Chlorthalidone, and Metoprolol succinate at 254 nm, 275 nm, and 224 nm, the linearity of the method was established. The calibration curve has five independent levels, ranging from 3-15 µg/ml of Telmisartan, 0.5-2.5 µg/ml of Chlorthalidone and 2-10 µg/ml of Metoprolol succinate were examined to determine the linearity [15]. For Telmisartan, Chlorthalidone and Metoprolol succinate, the following the acquisition of the calibration curve, the correlation coefficient and regression line equations were computed (Fig-12, 13, 14).

The Telmisartan, Chlorthalidone and Metoprolol succinate calibration curves were drawn at 254 nm, 275 nm and 224 nm (Fig-12, 13, 14). It was shown that the absorbance and the concentration of Telmisartan, Chlorthalidone and Metoprolol succinate at the wavelengths of 254 nm, 275 nm and 224 nm were linearly related, with ranges of 3-15 µg/ml, 0.5-2.5 µg/ml and 2-10 µg/ml in each case (Table. 1). The correlation coefficients demonstrated very strong linearity and the sample linear equations were computed using the least squares method.

Accuracy

The effectiveness of the procedure was evaluated using experiments that measured the percentage of three different levels of recovery (e.g., 50%, 80% and 100% accuracy). Standard solutions of metoprolol succinate, chlorthalidone, and telmisartan were added in known quantities to the pre-analyzed sample solutions. The following method was used to calculate the percentage recovery and measure absorbance after the medication quantities were established [16].

% Recovery = A-B/C×100

Where,

A - Shows how much medication should be taken in total,

B - Represents the quantity of material found through pre-analysis,

C - Similar to the quantity of added only pure drug.

High rate of recovery in the conventional addition method demonstrated the high accuracy of the suggested method. For Telmisartan, Chlorthalidone and Metoprolol succinate, the % of each drug recovered was found to be 95%, 92% and 96% respectively. The RSD was found to be 1.2%, 1.3% and 1.1% for Telmisartan, Chlorthalidone and Metoprolol succinate respectively (Table. 2).

Precision

In this intraday experiment, the drug concentration per replication was calculated three times in a single day. To express the laboratory variation during the day, the drug concentration was computed in an inter-day precision across a three-day period that followed one another. The percentage relative standard deviation (RSD) was computed in the methodologies for intra-day and inter-day precision studies [17].

The repeatability, intra-day, and inter-day measurement percentage relative standard deviation (%RSD) was calculated. It was discovered that these values were less than 2% RSD, indicating good precision (Table. 3).

Limit of detection (LOD) and quantification (LOQ)

The limit of quantification is the lowest concentration of analyte in a sample that can be quantitatively quantified with enough precision and accuracy, according to the International Council on Harmonization (ICH). In contrast, the limit of detection of an analytical method is the lowest amount of analyte in a sample that can be detected but not always quantitated as an exact value [18]. The average standard deviation and slope values were used to compute the limits of detection and quantification. The linearity investigations yielded the LOD and LOQ. The values were tabulated (Table. 4). The LOD and LOQ were calculated utilizing the formula below,

LOD = 3.3 × σ/slope

LOQ = 10 × σ/slope

Where, σ- Standard deviation

RESULTS & DISCUSSION

Simultaneous Equation Method

Calibration curve of Telmisartan, Chlorthalidone and Metoprolol succinate in methanol follows Beer's Lambert's Law. The graph of absorbance against concentration for Telmisartan, Chlorthalidone and Metoprolol succinate were found to be linear in the concentration range of 3-15 µg/ml, 0.5-2.5 µg/ml and 2-10 µg/ml respectively at 254 nm, 275 nm and 224 nm. The coefficient of regression of the calibration curve was found to be 0.999%. Regression equation gives the difference between a true value and approximate value. In the concentration range of Telmisartan (3-15 µg/ml), Chlorthalidone (0.5-2.5 µg/ml) and Metoprolol succinate (2-10 µg/ml) obeyed Beer's Law at 254 nm, 275 nm and 224 nm.

Linearity equation of Telmisartan, Chlorthalidone and Metoprolol succinate were shown in (fig-12, 13, 14). The lower magnitude of error (<2%) indicates a high prediction power of the regression equation. The results obtained for linearity are summarized in Table 1. Accuracy was calculated using % RSD value shown in Table 2. Precision was calculated as intra-day precision, inter-day precision and repeatability for both the drugs as shown in Table 3. LOD and LOQ are calculated based on the experimental data using appropriate statistical methods shown in Table 4.

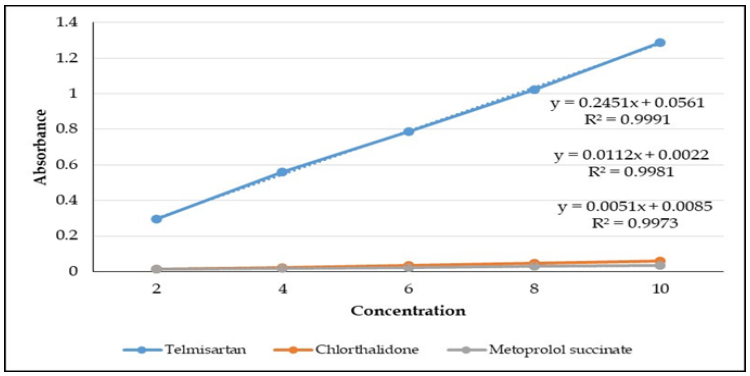

Figure-12: Linearity graph of Telmisartan, Chlorthalidone and Metoprolol succinate at 254 nm

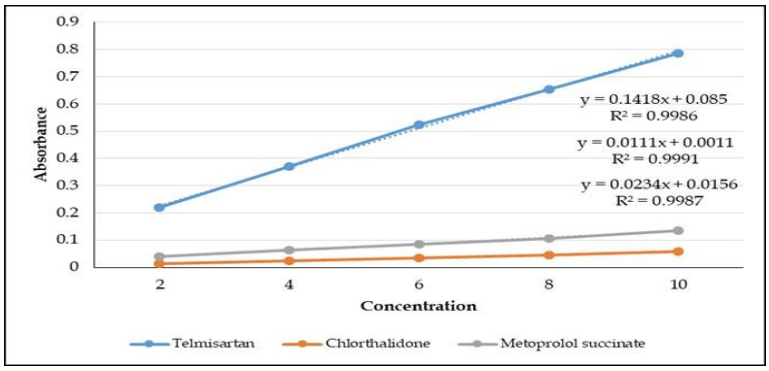

Figure-13: Linearity graph of Telmisartan, Chlorthalidone and Metoprolol succinate at 275 nm

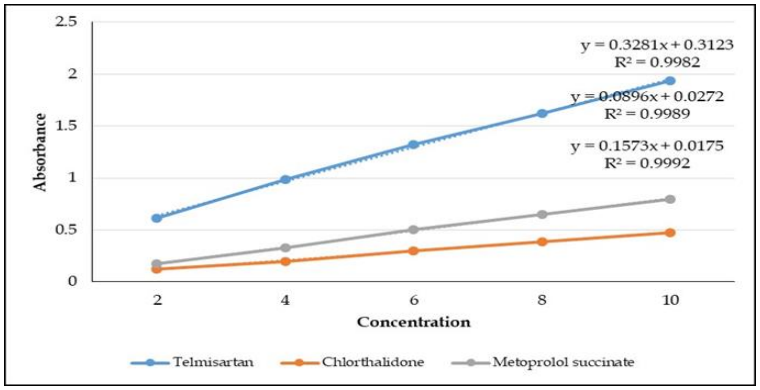

Figure-14: Linearity graph of Telmisartan, Chlorthalidone and Metoprolol succinate at 224nm

Table-1: Standard curve calibration point with % relative standard deviation (RSD) and standard deviation (SD)

Absorbance at 254 nm								
Telmisartan			**Chlorthalidone**			**Metoprolol succinate**		
Conc (µg/ml)	**Abs ± SD (n=3)**	**% RSD**	**Conc (µg/ml)**	**Abs ± SD (n=3)**	**% RSD**	**Conc (µg/ml)**	**Abs ± SD (n=3)**	**% RSD**
3	0.294 ± 0.001	0.34	0.5	0.014 ±0.0001	0.82	2	0.014 ± 0.0002	1.6
6	0.562 ± 0.001	0.19	1	0.024 ±0.0001	0.48	4	0.018 ± 0.0001	0.95
9	0.789 ± 0.001	0.21	1.5	0.036 ±0.0001	0.32	6	0.024 ± 0.0002	1.19
12	1.023 ± 0.002	0.25	2	0.046 ± 0.0005	1.26	8	0.029 ± 0.0004	0.59
15	1.288 ± 0.002	0.2	2.5	0.059 ± 0.001	1.72	10	0.034 ± 0.0002	0.84
Absorbance at 275 nm								
Telmisartan			**Chlorthalidone**			**Metoprolol succinate**		
Conc (µg/ml)	**Abs ± SD (n=3)**	**% RSD**	**Conc (µg/ml)**	**Abs ± SD (n=3)**	**% RSD**	**Conc (µg/ml)**	**Abs ± SD (n=3)**	**% RSD**
3	0.219 ± 0.001	0.45	0.5	0.012 ± 0.0001	1.43	2	0.039 ± 0.0001	0.29
6	0.370 ± 0.002	0.54	1	0.024 ± 0.0002	0.95	4	0.063 ± 0.001	1.58
9	0.523 ± 0.004	0.76	1.5	0.034 ± 0.0002	0.67	6	0.086 ± 0.001	1.74
12	0.654 ± 0.001	0.15	2	0.045 ± 0.0004	0.89	8	0.107 ± 0.002	1.86
15	0.786 ± 0.002	0.25	2.5	0.057 ± 0.001	1.75	10	0.134 ± 0.002	1.49
Absorbance at 224 nm								
Telmisartan			**Chlorthalidone**			**Metoprolol succinate**		
Conc (µg/ml)	**Abs ± SD (n=3)**	**% RSD**	**Conc (µg/ml)**	**Abs ± SD (n=3)**	**% RSD**	**Conc (µg/ml)**	**Abs ± SD (n=3)**	**% RSD**
3	0.615 ± 0.002	0.32	0.5	0.122 ± 0.001	0.81	2	0.171 ± 0.002	1.16
6	0.984 ± 0.004	0.4	1	0.199 ± 0.002	1	4	0.329 ± 0.002	0.6
9	1.325 ± 0.005	0.37	1.5	0.297 ± 0.002	0.67	6	0.501 ± 0.001	0.19

12	1.623 ± 0.002	0.12	2	0.385 ± 0.003	0.77	8	0.648 ± 0.001	0.15
15	1.936 ± 0.002	0.1	2.5	0.477 ± 0.002	0.42	10	0.798 ± 0.002	0.25

Table-2: Outcomes of studies on accuracy

Drug	Label claim (mg)	Amount found (mg)	% Label claim	% RSD*
Telmisartan	40	38	95	1.2
Chlorthalidone	12.5	11.5	92	1.3
Metoprolol succinate	25	24	96	1.1

* Relative Standard Deviation

Table-3: Outcomes of intra-day precision, inter-day precision and repeatability

Intra-day precision									
Level	**Telmisartan**			**Chlorthalidone**			**Metoprolol succinate**		
	Conc (µg/ml)	**Abs**	**% RSD**	**Conc (µg/ml)**	**Abs**	**% RSD**	**Conc (µg/ml)**	**Abs**	**% RSD**
1.	9	0.888	0.45	1.5	0.086	0.66	6	0.426	0.48
2.		0.891			0.086			0.430	
3.		0.896			0.087			0.429	
Inter-day precision									
Level	**Telmisartan**			**Chlorthalidone**			**Metoprolol succinate**		
	Conc (µg/ml)	**Abs**	**% RSD**	**Conc (µg/ml)**	**Abs**	**% RSD**	**Conc (µg/ml)**	**Abs**	**% RSD**
1.	9	0.895	0.28	1.5	0.081	0.7	6	0.425	0.72
2.		0.892			0.082			0.419	
3.		0.894			0.081			0.423	
Repeatability precision									
Level	**Telmisartan**			**Chlorthalidone**			**Metoprolol succinate**		
	Conc (µg/ml)	**Abs**	**% RSD**	**Conc (µg/ml)**	**Abs**	**% RSD**	**Conc (µg/ml)**	**Abs**	**% RSD**
1.	9	0.896	0.34	1.5	0.082	0.5	6	0.4234	0.46
2.		0.889			0.081			0.423	
3.		0.895			0.081			0.424	
4.		0.894			0.081			0.424	
5.		0.889			0.081			0.422	
6.		0.894			0.081			0.419	

Table-4: Results of LOD and LOQ

Drugs (Wavelength)	Parameters	
	LOD (µg/ml)	LOQ (µg/ml)
Telmisartan (254 nm)	0.5	1.6
Chlorthalidone (275 nm)	0.09	0.27
Metoprolol succinate (224 nm)	0.3	1.02

CONCLUSION

The UV spectrophotometric Simultaneous equation approach was developed and verified to perform the simultaneous estimate of Telmisartan, Chlorthalidone, and Metoprolol succinate. The method's simplicity, precision, repeatability, speed, and sensitivity were all shown by the combined results. The absorbance was determined to be linear in the range of 3–15 µg/ml, 0.5–2.5 µg/ml, and 2–10 µg/ml for Telmisartan, Chlorthalidone, and Metoprolol succinate, respectively, at both wavelengths of 254 nm, 275 nm, and 224 nm. Using the least squares technique, the sample linear equations were produced and the correlation coefficients demonstrated strong linearity. In order to generate data efficiently and create combination formulations of these three medications in the future, the simultaneous measurement of Telmisartan, Chlorthalidone and Metoprolol succinate in laboratory samples may be accomplished successfully and affordably with this method.

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