GREEN ANALYTICAL APPROACH FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND CHLORTHALIDONE IN COMBINED TABLET FORMULATION

Manoj Kumari More[1]*, Virendra Kumar Sharma[2]
[1]Research Scholar, School of Pharmacy, LNCT University, Bhopal (M.P.)
[2]Professor, School of Pharmacy, LNCT University, Bhopal (M.P.)
Corresponding Author mail id: manojkumarimore@gmail.com

Abstract
The present study was aimed at developing and validating a simple, accurate, precise, economical, and eco-friendly UV spectrophotometric method for the simultaneous estimation of Telmisartan (TMS) and Chlorthalidone (CTD) using mixed hydrotropic solubilization technique. Poor aqueous solubility of both drugs was successfully enhanced using a mixed hydrotropic solution containing 2M sodium citrate, 2M sodium benzoate, and 8M urea in the ratio of 1:1:1. The developed solvent system provided significant solubility enhancement along with good stability and spectral characteristics for both drugs. The λmax of TMS and CTD were found to be 216.0 nm and 232.0 nm, respectively. Beer-Lambert's law was obeyed in the concentration range of 5–25 µg/mL for TMS and 2–10 µg/mL for CTD with correlation coefficient values of 0.9990 and 0.9991, respectively. The simultaneous equation method was successfully applied for quantitative estimation of both drugs in combined tablet dosage form. The developed method was validated according to ICH guidelines for parameters including linearity, accuracy, precision, repeatability, reproducibility, and recovery studies. Recovery studies showed percentage recoveries in the range of 98–100%, indicating excellent accuracy of the method. Precision studies demonstrated low %RSD values, confirming good repeatability and reproducibility. The assay of marketed tablet formulation showed drug content close to the labeled claim with satisfactory precision. The proposed method was found to be simple, rapid, reliable, cost-effective, and suitable for routine quality control analysis of Telmisartan and Chlorthalidone in bulk and pharmaceutical dosage forms.

Keywords: Telmisartan, Chlorthalidone, Mixed Hydrotropy, UV Spectrophotometry, Simultaneous Equation Method, Method Validation, Solubility Enhancement, Pharmaceutical Analysis, ICH Guidelines, Quantitative Estimation.

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Introduction

Hypertension is one of the most common cardiovascular disorders worldwide and is considered a major risk factor for heart disease, stroke, renal failure, and other vascular complications [1-2]. Combination therapy is frequently employed in the management of hypertension to achieve better therapeutic efficacy and improved patient compliance. Telmisartan (TMS), an angiotensin-II receptor blocker (ARB), is widely used for the treatment of hypertension by selectively blocking angiotensin-II receptors, thereby reducing vasoconstriction and aldosterone secretion. Chlorthalidone (CTD) is a long-acting thiazide-like diuretic that lowers blood pressure by increasing sodium and water excretion. The combination of TMS and CTD provides synergistic antihypertensive action and is extensively used in the treatment of moderate to severe hypertension [3-4].

Analytical methods play an important role in the quality control and quantitative estimation of pharmaceutical formulations. Several analytical techniques such as HPLC, HPTLC, and UV spectrophotometry have been reported for the estimation of Telmisartan and Chlorthalidone either alone or in combination. Among these techniques, UV spectrophotometry is widely preferred because of its simplicity, rapidity, cost-effectiveness, and ease of operation [5-8].

However, the major limitation in UV analysis of Telmisartan and Chlorthalidone is their poor aqueous solubility, which often necessitates the use of organic solvents. The use of organic solvents increases the cost of analysis and may also pose environmental and toxicological hazards.

Hydrotropic solubilization is an effective and eco-friendly technique used to enhance the aqueous solubility of poorly water-soluble drugs by employing high concentrations of hydrotropic agents [9]. Hydrotropes such as sodium citrate, sodium benzoate, urea, sodium acetate, and other organic salts improve drug solubility without chemical modification of the drug molecule [10]. Mixed hydrotropy, involving a combination of different

hydrotropic agents, has been found to produce greater solubility enhancement compared with individual hydrotropes while minimizing the concentration-related side effects of a single hydrotropic agent [11]. In the present study, a mixed hydrotropic solution containing 2M sodium citrate, 2M sodium benzoate, and 8M urea in the ratio of 1:1:1 was utilized for simultaneous estimation of Telmisartan and Chlorthalidone by UV spectrophotometric method. The proposed method aimed to develop a simple, economical, accurate, precise, and environmentally safe analytical procedure without the use of expensive and toxic organic solvents. The developed method was validated according to ICH guidelines with respect to linearity, accuracy, precision, repeatability, reproducibility, and assay of marketed tablet formulation. The study highlights the applicability of mixed hydrotropic solubilization as a green analytical approach for routine pharmaceutical analysis of combined dosage forms containing Telmisartan and Chlorthalidone.

Material and Methods

Material

Telmisartan (TMS) and Chlorthalidone (CTD) were obtained as gift samples from a reputed pharmaceutical company. Sodium citrate, sodium benzoate, urea, sodium acetate, ammonium acetate, sodium salicylate, sodium tartrate, sodium succinate, potassium citrate, PEG 400, propylene glycol, methanol, ethanol, and other analytical grade chemicals and reagents were procured from standard chemical suppliers. Double distilled water was used throughout the study. Marketed tablet formulations containing Telmisartan and Chlorthalidone were purchased from the local market for analysis. UV-Visible spectrophotometer with matched quartz cells and other standard laboratory glassware were used during the experimental work.

Methods

Selection of Solvent System

Telmisartan (TMS) and Chlorthalidone (CTD) were scanned in various hydrotropic agents in the UV spectral range of 200–400 nm to identify a suitable solvent system for simultaneous estimation. Among the different hydrotropic systems evaluated, the mixed hydrotropic solution containing 2M sodium citrate, 2M sodium benzoate, and 8M urea in the ratio of 1:1:1 was found to be most appropriate. Both drugs exhibited good solubility and stability in this solvent system along with satisfactory spectral characteristics. The selected hydrotropic solution showed no interference at the λmax of either drug. Furthermore, the solvent system produced more than 18.97-fold enhancement in solubility for TMS and more than 14.06-fold enhancement for CTD compared to water, making it highly suitable for analytical application.

Establishment of Stability Profile

The stability of both drugs in the selected mixed hydrotropic solution was evaluated by preparing separate solutions of TMS and CTD at concentrations of 10µg/mL each. The solutions were scanned continuously under time scan mode for 30 minutes. The spectral data obtained during the study indicated that both drugs remained stable in the mixed hydrotropic solution without significant change in absorbance or spectral pattern throughout the scanning period.

Linearity Range and Calibration Curve

Standard stock solutions (Stock-A) of Telmisartan and Chlorthalidone were prepared separately by accurately weighing 100 mg of each drug and transferring them into separate 100 mL volumetric flasks. Approximately 80 mL of mixed hydrotropic solution containing 2M sodium citrate, 2M sodium benzoate, and 8M urea (1:1:1) was added to each flask. The solutions were sonicated for about 10 minutes to ensure complete solubilization of the drugs, and the volume was adjusted to 100 mL with the same solvent system to obtain stock solutions containing 1000 µg/mL of each drug.

Sub-stock solutions (Stock-B) were prepared by transferring 2.5 mL aliquots from the respective stock solutions into separate 25 mL volumetric flasks and diluting up to the mark with distilled water to obtain concentrations of 100 µg/mL. Working standard solutions of CTD were prepared by transferring aliquots of 0.2, 0.4, 0.6, 0.8, and 1.0 mL into separate 10 mL volumetric flasks and diluting with water to obtain concentrations of 2, 4, 6, 8, and 10 µg/mL, respectively. Similarly, working standard solutions of TMS were prepared by transferring 1.0, 2.0, 3.0, 4.0, and 5.0 mL aliquots into separate 10 mL volumetric flasks and making up the volume with water to obtain concentrations of 5, 10, 15, 20, and 25 µg/mL, respectively.

Selection of Wavelength for Linearity

Solutions containing 2 µg/mL of TMS and 20 µg/mL of CTD were prepared separately and scanned in the UV region between 200–400 nm. The maximum absorbance (λmax) of TMS and CTD was observed at 292.0 nm and 226.0 nm, respectively. Both drugs obeyed Beer-Lambert's law within the concentration range of 5–25 µg/mL for TMS and 2–10 µg/mL for CTD at their respective λmax values. Calibration curves were constructed by plotting absorbance against concentration, and good linearity was observed for both drugs.

Study of Overlay Spectra

Working standard solutions containing 2µg/mL of TMS and 20µg/mL of CTD were scanned in the UV

spectral range of 200–400 nm against water as blank, and the overlain spectra were recorded. TMS showed maximum absorbance at 292.0 nm, while CTD exhibited maximum absorbance at 226.0 nm. The overlay spectra also revealed an isoabsorptive point at 258.0 nm. Since both drugs showed distinct absorbance maxima without interference from one another, simultaneous estimation by the simultaneous equation method was considered suitable.

The simultaneous equation method is based on measurement of absorbance of two drugs at the λmax of each other. The selected wavelengths for analysis were 292.0 nm and 226.0 nm corresponding to λmax of TMS and CTD, respectively. Absorbances of the drug mixture were measured at both wavelengths, and absorptivity coefficients for each drug at both wavelengths were determined from five independent determinations. The concentrations of TMS and CTD in the sample were calculated using the following equations:

$$C\,TMS = \frac{A1ay2 - A2ay2}{ax1ay2 - ax2ay1} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.(1)$$

$$C\,CTD = \frac{A1ax2 - A2ax2}{ax1ay2 - ax2ay1} \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots Eq.(2)$$

Where, A_1 and A_2 are absorbances of mixture at 292.0 nm and 226.0 nm respectively, ax_1 and ax_2 are absorptivities of TMS at λ_1 (296.0 i.e. λ_{max} of TMS) and λ_2 (226.0 i.e. λ_{max} of CTD) respectively and ay_1 and ay_2 are absorptivities of CTD at λ_1 and λ_2 respectively. C_{CTD} and C_{TMS} are concentrations of TMS and CTD respectively. Fig. 6.7 represent the overlain spectra of both the drugs in 40:12.5 ratio and the criteria for obtaining maximum precision [i.e. absorbance ratio $(A_2/A_1)/ax_2/ax_1$ and ay_2/ay_1] by this method were calculated and found to be outside the range of 0.1-2.0 which is satisfied for both the TMS and CTD.

Validation of Simultaneous Equation Method [12]

Linearity

Linearity of both drugs was established using response ratio analysis. The response ratio for each concentration was calculated by dividing absorbance by the corresponding concentration. A graph of concentration versus response ratio was plotted, which confirmed linear response within the selected concentration ranges.

Accuracy

The accuracy of the proposed method was evaluated through recovery studies at three different levels, namely 80%, 100%, and 120%. Known quantities of standard TMS and CTD solutions were added to pre-analyzed tablet solutions, and the resulting mixtures were reanalyzed using the proposed method. Recovery studies were carried out in triplicate for each concentration level to determine the accuracy and reliability of the method.

Precision

Precision of the method was assessed in terms of repeatability, intermediate precision, and reproducibility. Repeatability was evaluated by analyzing the same concentration of both drugs five times under identical conditions. Intermediate precision was assessed by performing day-to-day and analyst-to-analyst studies using five different concentrations over three consecutive days. The results demonstrated good precision with low variability.

Analysis of Tablet Formulation

Twenty marketed tablets containing TMS and CTD were accurately weighed and finely powdered. Tablet powder equivalent to 10 mg of TMS was transferred into a 10 mL volumetric flask. The corresponding amount of CTD present in the powder was 3.125 mg. Approximately 8 mL of mixed hydrotropic solution containing 2M sodium citrate, 2M sodium benzoate, and 8M urea (1:1:1) was added, and the solution was sonicated for about 10 minutes to ensure complete solubilization of the drugs. The volume was then adjusted to the mark with the same hydrotropic solution. The resulting solution was filtered through Whatman filter paper No. 41, and suitable dilutions were prepared with distilled water to obtain concentrations within the working range. Absorbances of the final solutions were measured at the selected wavelengths, and the concentrations of both drugs were calculated using the simultaneous equation method. The analysis was repeated five times to ensure reproducibility and accuracy of the method.

Results and Discussion

The present study was carried out to develop and validate a simple, accurate, precise, and economical UV spectrophotometric method for the simultaneous estimation of Telmisartan (TMS) and Chlorthalidone (CTD) using mixed hydrotropic solubilization technique. Mixed hydrotropy was successfully employed to enhance the aqueous solubility of both poorly water-soluble drugs without the use of organic solvents, thereby making the method environmentally friendly and cost-effective.

Different hydrotropic agents and their combinations were evaluated for solubility enhancement of TMS and CTD. Among all the investigated systems, the mixed hydrotropic solution containing 2M sodium citrate, 2M sodium benzoate, and 8M urea in the ratio of 1:1:1 was found to be the most suitable solvent system. This combination provided significant enhancement in solubility for both drugs along with good spectral characteristics and stability. The

solubility enhancement observed for TMS and CTD confirmed the effectiveness of the mixed hydrotropic approach for analytical applications.

The λmax values of both drugs were determined by scanning the drug solutions in the UV region of 200–400 nm. TMS exhibited maximum absorbance at 216.0 nm, while CTD showed λmax at 232.0 nm as shown in Figure 1. The overlay spectra demonstrated adequate spectral separation and the presence of isoabsorptive characteristics, which enabled simultaneous estimation of both drugs without interference, as represented in Figure 3.

Linearity studies demonstrated that both drugs obeyed Beer-Lambert's law within the selected concentration ranges. TMS showed linearity in the range of 5–25 µg/mL, whereas CTD exhibited linearity in the range of 2–10 µg/mL. The regression equations and correlation coefficient values presented in Table 1 indicated excellent linear relationships between concentration and absorbance for both drugs. The correlation coefficient values of 0.9990 for TMS and 0.9991 for CTD confirmed the reliability and suitability of the developed method for quantitative estimation. Low standard deviation and %RSD values further indicated good consistency of the analytical data. The calibration curve of CTD is represented in Figure 2.

Accuracy of the developed method was evaluated through recovery studies at 80%, 100%, and 120% levels. The results summarized in Table 2 showed percentage recoveries close to 100% for both drugs, indicating excellent accuracy of the proposed method. TMS showed mean recoveries ranging from 98.81% to 99.07%, while CTD exhibited recoveries between 98.13% and 98.97%. The low SD and %RSD values confirmed that the method was free from interference of excipients and capable of accurate drug estimation.

Precision studies were performed in terms of repeatability, day-to-day precision, analyst-to-analyst precision, and reproducibility. The validation results summarized in Table 3 demonstrated low %RSD values for all precision parameters, which were well within acceptable limits. Repeatability studies showed %RSD values of 0.118 for TMS and 0.050 for CTD, indicating excellent method precision. Similarly, day-to-day precision, analyst-to-analyst variation, and reproducibility studies also produced satisfactory results with low variability. These findings confirmed that the developed UV spectrophotometric method is highly precise and reproducible.

The developed method was successfully applied for the analysis of marketed tablet formulation containing TMS and CTD. The assay results shown in Table 4 demonstrated that the percentage label claim for TMS and CTD was found to be 99.63% and 99.60%, respectively. The low SD and %RSD values indicated excellent uniformity and reliability of the method for routine quality control analysis of pharmaceutical dosage forms.

The developed mixed hydrotropic UV spectrophotometric method proved to be simple, rapid, accurate, precise, economical, and environmentally safe for simultaneous estimation of Telmisartan and Chlorthalidone in combined tablet dosage form. The method eliminated the use of costly and toxic organic solvents and can therefore be effectively utilized for routine pharmaceutical analysis and quality control studies.

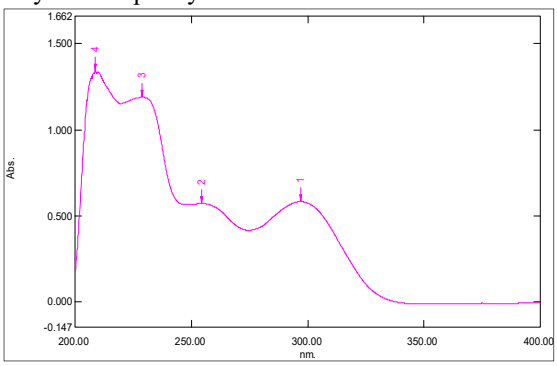

Figure 1: Determination of λ_{max} of TMS

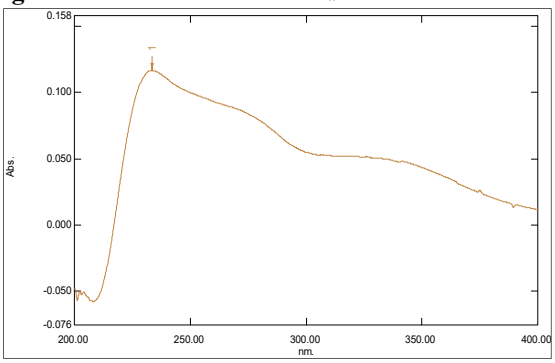

Figure 2: Linearity of CTD

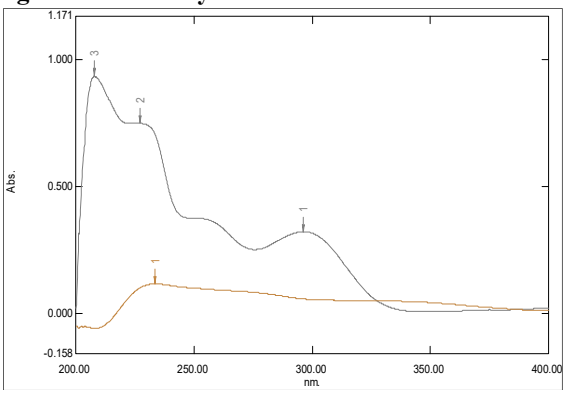

Figure 3: Overlay Spectra of TMS and CTD

Table 1: Statistical Data for Linearity of TMS and CTD

S.	Parameter	TMS	CTD

No.			
1	λmax	216.0 nm	232.0 nm
2	Beer's law range	5–25 µg/mL	2–10 µg/mL
3	Regression equation	y = 0.0507x + 0.016	y = 0.0607x – 0.0025
4	Slope	0.0507	0.0607
5	Intercept	0.016	-0.0025
6	Correlation coefficient (R^2)	0.9990	0.9991
7	Standard deviation range	0.001 – 0.002	0.001 – 0.002
8	% RSD range	0.089 – 0.305	0.199 – 0.674

Table 2: Recovery Study Data for TMS and CTD

S. No.	Drug	Recovery Level	Mean Recovery (%)	SD	% RSD
1	TMS	80%	99.07	0.368	0.371
2	TMS	100%	99.07	0.368	0.371
3	TMS	120%	98.81	0.698	0.706
4	CTD	80%	98.97	0.479	0.484
5	CTD	100%	98.13	0.994	1.013
6	CTD	120%	98.89	0.490	0.496

Table 3: Results of Validation parameters

Validation Parameter	Drug	Mean (%)	S.D.	% R.S.D.
Repeatability	TMS	98.279	0.115	0.118
Repeatability	CTD	98.882	0.049	0.050
Day-to-Day Precision	TMS	99.252	0.076	0.077
Day-to-Day Precision	CTD	98.865	0.041	0.042
Analyst-to-Analyst Precision	TMS	98.699	0.099	0.100
Analyst-to-Analyst Precision	CTD	97.751	0.106	0.109
Reproducibility	TMS	98.684	0.104	0.105
Reproducibility	CTD	98.281	0.077	0.079

Table 4: Analysis of tablet formulation of TMS and CTD

Drugs	Label claim (mg)	Amount found (mg)	Label claim (%)	S.D.	% RSD
TMS	40	39.85	99.63	0.125	0.245
CTD	12.5	12.45	99.60	0.226	0.369

Conclusion

The developed mixed hydrotropic UV spectrophotometric method for simultaneous estimation of Telmisartan and Chlorthalidone was found to be simple, accurate, precise, economical, and eco-friendly. The mixed hydrotropic solution effectively enhanced the solubility of both poorly water-soluble drugs without the use of organic solvents. The method showed excellent linearity, accuracy, precision, and reproducibility as per ICH guidelines. The assay results of marketed tablet formulation were within acceptable limits, confirming the suitability of the method for routine pharmaceutical analysis and quality control of combined dosage forms containing Telmisartan and Chlorthalidone.

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Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this manuscript.

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