RESEARCH PAPER

METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND AMLODIPINE IN FIXED DOSE COMBINATION USING HYDROTROPY PHENOMENA

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ABSTRACT
A simple, accurate, precise, economical, and eco-friendly UV spectrophotometric method was developed and validated for the simultaneous estimation of Telmisartan and Amlodipine in fixed dose combination tablet dosage form using the hydrotropic solubilization phenomenon. Due to poor aqueous solubility of both drugs, a mixed hydrotropic solution containing 1M Sodium salicylate and 1M Nicotinamide in the ratio of 1:1 was employed to enhance solubility and avoid the use of organic solvents. The maximum absorbance of Telmisartan and Amlodipine was observed at 234 nm and 259 nm respectively. Simultaneous equation method was applied for quantitative estimation of both drugs. Telmisartan and Amlodipine obeyed Beer-Lambert's law in the concentration ranges of 10–50 µg/ml and 2–10 µg/ml respectively. The developed method was validated according to ICH guidelines for parameters such as linearity, accuracy, precision, and reproducibility. The correlation coefficient values were found to be 0.9968 for Telmisartan and 0.9995 for Amlodipine, indicating good linearity. Recovery studies showed percentage recoveries within acceptable limits, confirming the accuracy of the method. Precision studies demonstrated low standard deviation and %RSD values, indicating reliability and reproducibility of the method. The proposed method was successfully applied for the analysis of marketed tablet formulations and was found suitable for routine quality control analysis of Telmisartan and Amlodipine in combined dosage forms.

Keywords: Hydrotropy, UV spectrophotometry, Simultaneous equation method, Telmisartan, Amlodipine, Method validation, Mixed hydrotropic agent, Pharmaceutical analysis.
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Introduction

Hypertension is one of the most prevalent cardiovascular disorders worldwide and is considered a major risk factor for stroke, myocardial infarction, renal failure, and other cardiovascular complications.[1] Combination therapy is commonly employed in the management of hypertension to achieve better therapeutic efficacy and improved patient compliance.[2] The fixed dose combination of Telmisartan and Amlodipine is widely prescribed for the treatment of hypertension due to their complementary mechanisms of action.[3]

Telmisartan is an angiotensin II receptor blocker (ARB) that selectively inhibits the binding of angiotensin II to the AT1 receptor, thereby reducing vasoconstriction and aldosterone secretion.[4] Amlodipine is a calcium channel blocker belonging to the dihydropyridine class that acts by inhibiting the influx of calcium ions into vascular smooth muscle cells, resulting in vasodilation and reduction in blood pressure. The synergistic action of these drugs provides enhanced antihypertensive activity with reduced adverse effects.[5]

Simultaneous estimation of Telmisartan and Amlodipine in combined pharmaceutical dosage forms is essential for quality control and assurance of the formulation. Various analytical methods such as UV spectrophotometry, HPLC, HPTLC, and LC-MS have been reported for the determination of these drugs either individually or in combination. However, many of these methods involve the use of large quantities of organic solvents, complex sample preparation procedures, high analysis cost, and environmental concerns.[6-9]

Hydrotropy is a solubilization technique in which the aqueous solubility of poorly water-soluble drugs is enhanced by the addition of a large amount of hydrotropic agents such as sodium benzoate, sodium citrate, urea, or sodium salicylate.[10] The hydrotropic phenomenon offers several advantages including eco-friendly analysis, reduction in the use of toxic organic solvents, cost-effectiveness, simplicity, and improved analytical accuracy.[11] Since Telmisartan exhibits poor aqueous solubility, hydrotropic solubilization can serve as an effective approach for its quantitative estimation along with Amlodipine.[12-13]

Therefore, the present study aims to develop and validate a simple, accurate, precise, economical, and reproducible analytical method for the simultaneous estimation of Telmisartan and Amlodipine in fixed dose combination using the hydrotropy phenomenon. The developed method is validated according to ICH guidelines with respect to parameters such as linearity, accuracy, precision, robustness, limit of detection, and limit of quantification to ensure its suitability for routine pharmaceutical analysis.

Material and Methods

Material

Pure drug samples of Telmisartan and Amlodipine were obtained as gift samples from reputed pharmaceutical industries. Marketed tablet formulations containing Telmisartan 40 mg and Amlodipine 5 mg were procured from the local market for analysis. Sodium salicylate and Nicotinamide used as hydrotropic agents were of analytical reagent grade. RO water was used throughout the study for preparation and dilution of solutions. Whatman filter paper No. 41 was used for filtration purposes. All chemicals and reagents used in the study were of analytical grade and utilized without further purification.

Methods

The combination of Telmisartan and Amlodipine has been recently introduced in the pharmaceutical market in the ratio of 5:40 mg for the effective management of hypertension associated with diabetes mellitus. Telmisartan, an angiotensin II receptor blocker, and Amlodipine, a calcium channel blocker, act synergistically to provide better blood pressure control and reduce cardiovascular complications. Literature survey revealed that, till date, no spectrophotometric method has been reported for the simultaneous estimation of Telmisartan and Amlodipine in combined dosage form using the hydrotropic solubilization phenomenon. Therefore, the present work was undertaken to develop a simple, economical, accurate, and eco-friendly spectrophotometric method employing hydrotropic agents for the simultaneous estimation of both drugs in marketed tablet formulations.

Solubility Study

The solubility of Telmisartan and Amlodipine was determined at 25±1°C using different solvents. Accurately weighed quantities of 10 mg of each drug were transferred separately into 10 ml volumetric flasks containing various solvents and subjected to mechanical shaking for 8 hours. After shaking, the solutions were filtered through Whatman filter paper No. 41 and analyzed visually after suitable dilution. Among the various hydrotropic systems investigated, a mixed hydrotropic solution containing 1M Sodium salicylate and 1M Nicotinamide in the ratio of 1:1 was found to be the most suitable solvent system because both drugs exhibited good solubility, stability, and satisfactory spectral characteristics in this medium without any interference at their respective absorption maxima. The mixed hydrotropic solution enhanced the solubility of Telmisartan by more than 26 folds and Amlodipine by more than 29 folds.

Selection of Solvent System

Telmisartan and Amlodipine were scanned in various hydrotropic agents over the UV range of 200–400 nm. Among the different solvent systems evaluated, 1M Sodium salicylate and 1M Nicotinamide in the ratio of 1:1 was found to be the most appropriate hydrotropic system because both drugs were highly soluble and stable in this medium. In addition, both drugs showed good spectral characteristics and the hydrotropic solution did not interfere at the λmax of either drug, making it suitable for simultaneous spectrophotometric estimation.

Preparation of Standard Stock Solution

Standard stock solutions were prepared by dissolving separately 100 mg of each drug in 80 ml of mixed hydrotropic solution containing Sodium salicylate and Nicotinamide (1:1). The solutions were sonicated for about 10 minutes to achieve complete solubilization and the volume was adjusted to 100 ml with the same hydrotropic solution to obtain stock solutions having concentration of 1000 µg/ml.

Preparation of Sub-Stock Solution

Further, 2.5 ml aliquots from each stock solution were transferred separately into 25 ml volumetric flasks and diluted up to the mark with RO water to obtain sub-stock solutions containing 100 µg/ml of each drug.

Preparation of Working Standard Solutions

Working standard solutions for Telmisartan were prepared by transferring aliquots of 0.2 ml, 0.4 ml, 0.6 ml, 0.8 ml, and 1.0 ml from the sub-stock solution into separate 10 ml volumetric flasks and diluting up to the mark with RO water to obtain concentrations ranging from 2–10 µg/ml. Similarly, working standard solutions of Amlodipine were prepared by transferring aliquots of 1.0 ml, 2.0 ml, 3.0 ml, 4.0 ml, and 5.0 ml into separate 10 ml volumetric flasks and making up the volume with RO water to obtain concentrations ranging from 5–25 µg/ml.

Selection of Wavelength for Linearity

The prepared solutions were scanned in the UV range of 200–400 nm for wavelength selection. Telmisartan exhibited maximum absorbance at 234.0 nm whereas Amlodipine showed maximum absorbance at 259.0 nm. Both drugs obeyed Beer-Lambert's law within

their respective concentration ranges. Calibration curves were plotted between absorbance and concentration for both drugs.

Study of Overlay Spectra

Overlay spectra of Telmisartan and Amlodipine demonstrated an isoabsorptive point at 220.0 nm and showed no spectral interference with each other, indicating suitability for simultaneous estimation by the simultaneous equation method. The simultaneous equation method was based on measurement of absorbance of both drugs at 234.0 nm and 259.0 nm. Absorptivity coefficients for both drugs at selected wavelengths were determined and used for calculation of concentrations of Telmisartan and Amlodipine in the formulation. The absorbance ratio and absorptivity ratio values were found to be within the acceptable range, confirming the precision and applicability of the method for simultaneous analysis.

Validation of developed method [14]

Linearity

Linearity of the developed method was established by plotting concentration versus response ratio for both drugs. The response ratio was calculated by dividing absorbance by the corresponding concentration. The method showed good linearity over the selected concentration ranges for both drugs.

Accuracy

Accuracy of the proposed method was evaluated by recovery studies using standard addition technique at 80%, 100%, and 120% levels. Known quantities of standard Telmisartan and Amlodipine were added to pre-analyzed tablet samples and the mixtures were reanalyzed. The recovery studies were performed in triplicate and the percentage recoveries obtained confirmed the accuracy 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 drug solution five times under identical conditions. Intermediate precision was studied by performing day-to-day and analyst-to-analyst variations using different concentrations over three consecutive days. The low percentage relative standard deviation values obtained indicated good precision of the developed method.

Analysis of Tablet Formulation

For analysis of marketed tablet formulation, twenty tablets containing Telmisartan and Amlodipine were accurately weighed and finely powdered. Tablet powder equivalent to 20 mg of Telmisartan and 1 mg of Amlodipine was transferred into a 10 ml volumetric flask. About 8 ml of mixed hydrotropic solution containing 1M Sodium salicylate and 1M Nicotinamide (1:1) was added and the mixture was sonicated for 10 minutes to ensure complete extraction of the drugs. The volume was then adjusted to the mark with hydrotropic solution and filtered through Whatman filter paper No. 41. Suitable dilutions were made with RO water to obtain concentrations within the working range. The absorbances were recorded at selected wavelengths and concentrations of both drugs were calculated using simultaneous equations. The analysis was repeated five times and satisfactory results were obtained, indicating suitability of the developed hydrotropic spectrophotometric method for routine quality control analysis of Telmisartan and Amlodipine in combined dosage forms.

Results and Discussion

The present study was aimed at developing a simple, accurate, precise, and economical UV spectrophotometric method for the simultaneous estimation of Telmisartan and Amlodipine in combined tablet dosage form using the hydrotropic solubilization phenomenon. The use of mixed hydrotropic agents successfully enhanced the aqueous solubility of both drugs and eliminated the requirement for organic solvents, thereby making the method eco-friendly and cost-effective.

The UV absorption spectrum of Telmisartan showed maximum absorbance at 234 nm as represented in Figure 1, whereas Amlodipine exhibited maximum absorbance at 259 nm. The overlay spectra of both drugs presented in Figure 3 demonstrated distinct absorption maxima with minimal spectral interference and also showed the presence of an isoabsorptive point at 220 nm. These spectral characteristics confirmed the suitability of the simultaneous equation method for quantitative estimation of both drugs in combined dosage forms.

The calibration curves constructed for both drugs showed good linearity within the selected concentration ranges. Telmisartan exhibited linearity in the concentration range of 10–50 µg/ml, while Amlodipine showed linearity in the range of 2–10 µg/ml. The linearity profile of Amlodipine is shown in Figure 2. The regression analysis data presented in Table 1 indicated high correlation coefficient values of 0.9968 for Telmisartan and 0.9995 for Amlodipine, demonstrating excellent linear relationship between concentration and absorbance. The slope and intercept values further confirmed the reliability and sensitivity of the developed analytical method.

The accuracy of the proposed method was evaluated by recovery studies at 80%, 100%, and 120% levels and the results are summarized in Table 2. The percentage recoveries for both drugs were found to

be within acceptable limits, ranging from 98.61% to 99.16% for Telmisartan and 98.08% to 99.01% for Amlodipine. The low standard deviation values indicated that the method was accurate and free from interference due to formulation excipients.

Precision studies were carried out in terms of repeatability, day-to-day variation, analyst-to-analyst variation, and reproducibility, and the results are shown in Table 3. The percentage assay values obtained for both drugs were close to 100% with low standard deviation values, indicating good precision and reproducibility of the developed method. The low %RSD values confirmed that the method produced consistent and reliable results during routine analysis.

The developed method was successfully applied for the analysis of marketed tablet formulation containing Telmisartan and Amlodipine. The assay results summarized in Table 4 showed percentage label claims of 97.38% for Telmisartan and 98.40% for Amlodipine. The low standard deviation and percentage relative standard deviation values indicated good agreement between the experimental results and the labeled claim of the formulation.

The developed hydrotropic UV spectrophotometric method proved to be simple, rapid, accurate, precise, economical, and suitable for routine quality control analysis of Telmisartan and Amlodipine in combined pharmaceutical dosage forms without the use of expensive organic solvents.

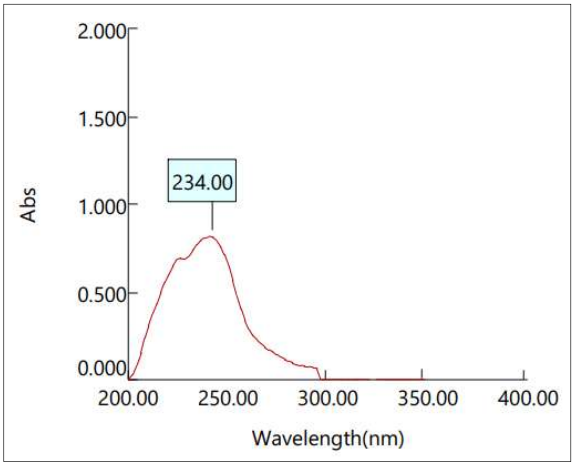

Figure 1: Determination of λ_{max} of TMS

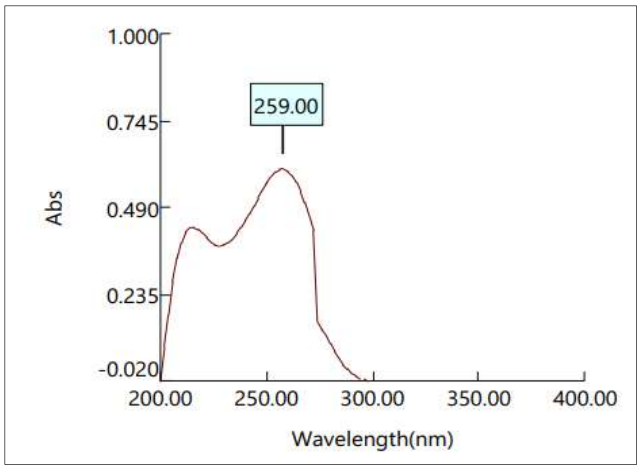

Figure 2: Linearity of AMD

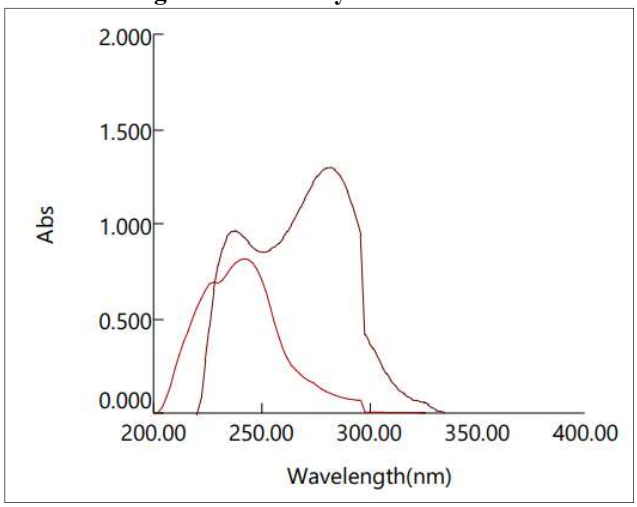

Figure 3: Overlay Spectra of Telmisartan and Amlodipine

Table 1: Results of Linearity of Telmisartan and Amlodipine

	Method	
Parameter	**TMS**	**AMD**
Working λ_{max}	234 nm	259 nm
Beer's law limit (µg/ml)	10-50	2-10
Correlation Coefficient (r^2)*	0.9968	0.9995
Slope (m)*	0.0202	0.0936
Intercept (c)*	0.0209	0.0041

Table 2: Results of Recovery Studies on Marketed Formulations

Recovery Level %	**% Recovery (Mean±SD)***	
	TMS	**AMD**
80	98.61±0.793	99.01±0.524
100	98.73±0.377	98.08±1.498
120	99.16±0.741	99.01±0.473

*Average of three determination

Table 3: Results of validation (Mean±SD)*

Parameter		Method	
		TMS	AMD
Precision*	Repeatability	99.053±0.111	97.024±0.100
	Day-to-Day	99.592±0.015	97.814±0.062
	Analyst-to-Analyst	99.066±0.041	99.235±0.151
	Reproducibility	99.504±0.114	97.649±0.080

*Average of five determination

Table 4: Analysis of Tablet Formulation of Telmisartan and Amlodipine

Drug	Label claim (mg)	Amount found (mg)	Label claim (%)	S.D.	% RSD
TMS	40	38.95	97.38	0.225	0.245
AMD	5	4.92	98.40	0.215	0.268

Conclusion

The present study successfully developed and validated a simple, accurate, precise, economical, and eco-friendly UV spectrophotometric method for the simultaneous estimation of Telmisartan and Amlodipine in fixed dose combination tablet dosage forms using the hydrotropic solubilization phenomenon. The mixed hydrotropic solution containing Sodium salicylate and Nicotinamide effectively enhanced the solubility of both drugs, thereby eliminating the need for costly and toxic organic solvents. The developed method showed good linearity, accuracy, precision, and reproducibility in accordance with ICH guidelines. Recovery and precision studies confirmed the reliability of the method for routine pharmaceutical analysis. The assay results of marketed formulations were found to be within acceptable limits, indicating suitability of the proposed method for routine quality control analysis of Telmisartan and Amlodipine in combined dosage forms.

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