STM JOURNALS

Research & Reviews: A Journal of
Drug Design & Discovery

ISSN: 2349-9036
Volume 11, Issue 1, 2024
January–April
DOI (Journal): 10.37591/RRJoDDD

https://journals.stmjournals.com/rrjoddd/

Research RRJoDDD

Simultaneous Determination and Stability Indicating Method for Telmisartan, Metoprolol Succinate and Cilnidipine in Tablet Dosage Form

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Abstract

*There are several medicinal agents available for antihypertensive activity. Telmisartan, metoprolol and cilnidipine are among them. Quantitative and qualitative analysis plays a pivotal role in safeguarding patients. Here, the estimation of these drugs was performed by using the chromatographic technique RP-HPLC. It was conducted with Phosphate buffer (pH 3.5 ± 0.01): Methanol (50:50 v/v) mobile phase. The system was operated at 1 ml/min. Drug volume to the system was 20µl. The column as a stationary Phase was C18, Hypersil BDS with 250 mm*4.6 mm dimension. In the experimental section, linearity and range were kept between 20 to 60 µg/ml for telmisartan, 5 to 15 µg/ml for cilnidipine, and 25 to 75 µg/ml for metoprolol. The drugs were eluted at 3.4, 4.1, and 11.5 min. for telmisartan, metoprolol, and Cilnidipine, respectively. The accuracy study was found to be 98.32 to 101.57% for all three drugs. % RSD value of the repeatability study was less than 2%. The determination of drugs was conducted at 215 nm. The method was also applied to pharmaceutical dosage forms. The proposed study was validated by ICH guidelines. The proposed study also extended for degradation protocol for all the drugs. The drugs were exposed to various conditions including acidic, basic, oxidation, thermal, and photolytic. The force degradation had shown more degradation in oxidative condition, 35.98% for telmisartan while 29.07% and 36.67% in basic condition for metoprolol succinate and cilnidipine, respectively. The very least degradation had been observed in photolytic conditions. It was 13.11%, 14.39%, and 15.25% for telmisartan, metoprolol and cilnidipine, respectively. The validated procedure would have applications regarding stability indicating, impurity separation, and qualitative and quantitative estimation of telmisartan, metoprolol, and cilnidipine in the solid dosage form.*

Keywords: Telmisartan, metoprolol, cilnidipine, HPLC, validation, degradation

INTRODUCTION

Telmisartan (TEL), metoprolol (MET) succinate, and cilnidipine (CIL) are widely used cardiovascular drugs. They can be categorized as angiotensin II receptor blockers, beta-blockers, and calcium channel blockers. These formulations play pivotal roles in the management of cardiovascular disease-related conditions.

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Received Date: April 01, 2024
Accepted Date: April 05, 2024
Published Date: April 15, 2024

Citation: Bhavesh Patel. Simultaneous Determination and Stability Indicating Method for Telmisartan, Metoprolol Succinate and Cilnidipine in Tablet Dosage Form. Research & Reviews: A Journal of Drug Design & Discovery. 2024; 11(1): 32–38p.

The IUPAC name for TEL, MET, and CIL is as follow, respectively, 4'-[(1,7'-dimethyl-2'-propyl-1H, 3'H-2, 5'-bibenzimidazol-3'-yl)methyl] biphenyl-2-carboxylic acid, 1-(isopropylamino)-3-[p-(2-methoxyethyl) phenoxy]-2-propanol succinate, 3-*O*-(2-methoxyethyl) 5-*O*-[(*E*)-3-phenylprop-2-enyl] 2, 6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3, 5-dicarboxylate.

TEL and CIL drugs are water-insoluble, but MET is water-soluble, while all drugs are freely soluble in methanol and acetonitrile. The molecular weights of TEL, MET, and CIL, respectively [1–3].

The simultaneous estimation and degradation of these drugs are essential for quality control, pharmacokinetic studies, and bioavailability assessments during clinical trials. Analytical methods that allow for their quantification in combination are valuable for pharmaceutical research and development.

This study aimed to develop a robust, accurate, sensitive, and reliable analytical method for the simultaneous determination of TEL, MET, and CIL. A literature review suggested that various methods, such as UV spectrophotometry [4–7], high-performance liquid chromatography (HPLC) [8–12], and HPTLC [13–14], can be used for estimation; however, the proposed method is superior and advantageous over them in terms of sensitivity and retention time, mean minute amount can be detected, lower retention time saves solvents and makes the detection rapid.

The successful development of such a method will contribute to better patient care by ensuring accurate dosing and minimizing adverse effects associated with polypharmacy.

MATERIALS AND METHODS

Pure powder of all drugs (5 g) was procured from Acron Pharmaceuticals, Ahmedabad, India. Arbitel-Trio 50 extended-release tablet formulation (Microlabs, India) was purchased from a local pharmacy. Methanol, Water, Ammonium acetate, and potassium dihydrogen phosphate were used during method development. HPLC grade solvents, throughout the study, were used and purchased from, SD Fine Chem, Vadodara, India.

The following instruments were used to develop and validate the proposed method: HPLC (LC-1020C HT) with a UV detector and autosampler, Shimadzu, Japan; pH meter and ultrasonicator, Systronics, Ahmedabad; digital balance, Sartorious, Japan.

Chromatographic Conditions

Different combinations of mobile phases were injected into the HPLC system, but the chromatographic conditions yielded an acceptable chromatogram. The optimized mobile phase was phosphate buffer (pH 3.5 ± 0.01): methanol (50:50 v/v) at a flow rate of 1 ml/min., injection volume of 20 µL, and stationary phase C18, Hypersil BDS with dimensions of 250 mm*4.6 mm. The drugs were eluted at a wavelength of 215 nm.

Preparation of Stock Solution

The pure powder was weighed with a quantity of TEL (40 mg), MET (50 mg), and CLI (10 mg) in a 100 ml. Dilution was performed to the mark with methanol to obtain 400 µg/ml, 500 µg/ml, and 100 µg/ml TEL, MET, and CLI, respectively.

Working Standard Solution

An aliquot of 1 ml was transferred from a stock solution of TEL, MET, and CLI to a 10 ml volumetric flask. It was diluted to the mark with the mobile phase to prepare TEL (40 µg/ml), MET (50 µg/ml), and CLI (10 µg/ml).

Method Validation

Linearity and Range

Aliquots of 0.5, 0.75, 1.0, 1.25, and 1.5 ml were transferred to a 10 ml volumetric flask from working standard solution to have a concentration of 2 to 6 µg/ml for TEL, 0.5 to 1.5 µg/ml for MET and 2.5 to 7.5 µg/ml for CLI. All solutions were injected into the system, and measurements were performed in triplicate to obtain the calibration curve of concentration vs. area under curve (AUC).

Precision

Intra-day precision was determined for three concentrations in the given range (n=3) at three different concentrations on the same day. This was performed for lower, middle, and higher concentrations of TEL, MET, and CLI, respectively. Lower concentrations were TEL (2 µg/ml), MET (0.5 µg/ml), and CIL (2.5 µg/ml), middle concentrations were TEL (4 µg/ml), MET (1.0 µg/ml), CLI (5.0 µg/ml) while higher concentrations were TEL (6 µg/ml), MET (1.5 µg/ml) and CLI (7.5 µg/ml). The results are reported as % RSD.

Inter-day precision: Inter-day precision was performed for three concentrations of the given range on day 1, day 2, and day 3. Lower, middle, and higher concentrations were selected as per the inter-day study.

System suitability (repeatability): This parameter was performed with six injections of the same concentration solution to establish the repeatability of the method. It was performed by selecting the middle concentration range for TEL (4.0 µg/ml), MET (1.0 µg/ml), and CLI (5.0 µg/ml).

Accuracy: This validation parameter was determined using a standard addition method. Standard working solutions were added to the sample solutions at 80%, 100%, and 120% of the selected concentration levels. A solution volume of 0.5 ml for each drug was transferred to 100 ml volumetric flasks. Sample solutions (0.4, 0.5, and 0.6 ml were then added to the respective flasks.

Limit of Detection and Limit of Quantification

The limit of detection (LOD) and limit of quantification (LOQ) can be calculated by several methods; however, in this study, they were calculated using the following equations:

$LOD = 3.3 \times N/S$ and

$LOQ = 10 \times N/S$.

Where, N = standard deviation of the peak areas of the drug and

S = slope of the corresponding calibration curve.

Robustness: This study was performed by deliberately changing the flow rate (± 0.1 ml), pH (± 0.1 ml), wavelength (± 0.5), and mobile phase composition (± 2.5 ml for each component).

Specificity: The specificity of an analytical method shows that it can measure the analyte of interest accurately and precisely without interference from the blank and placebo. Specific research was conducted to demonstrate that the presence of excipients did not affect the procedure.

Assay preparation: Marketed formulation was procured with Label claim:
TEL 40 mg, CIL 10 mg, and MET 50 mg.

Sample Solution

Accurately weighed 20 tablets were then powdered. The tablet powder (equivalent to 40 mg of TEL,10 mg of CIL, and 50 mg of MET) was transferred into a 100 ml volumetric flask, and a 60 ml mobile phase was added. The flask was shaken for 15 min, sonicated for 5 min, and the final volume was made up to 100 mL with a mobile phase. The filtered solution with Whatman filter paper (TEL 40 µg/ml, CIL-10 µg/ml, MET-50 µg/ml) was further diluted into another 10 ml volumetric flask to obtain TEL 4 µg/ml, CIL-1 µg/ml, and MET-5 µg/ml.

FORCE DEGRADATION STUDIES

Hydrolysis Degradation

Hydrolysis with 0.1 N NaOH and HCl (0.1 N) was carried out with concentrations of TEL (4 µg/ml), CIL (1 µg/ml), and MET (5 µg/ml) by exposing the drugs with 0.1N HCl and 0.1 N NaOH solution for 40 min. Degradation was documented by comparing the AUC with the standard chromatogram area for all three drugs.

Oxidative Degradation

Hydrogen peroxide (H_2O_2) was used as the oxidizing agent to perform the degradation experiments. The drugs were dissolved in 3% hydrogen peroxide and evaluated after 40 min. interval of time.

Thermal Degradation

For thermal degradation, a temperature of 45°C was set for the hot-air oven. The drugs were then administered for 40 min. and estimated the % degradation.

Photolytic Degradation

Drugs were exposed to UV light for up to 4 h, and solutions were prepared for the determination of photolytic degradation.

Method Validation

Selection of wavelength: The solution with a concentration of 10 µg/ml was scanned using a UV Spectrophotometer in the 200–400 nm range, and an overlay graph was obtained to optimize the wavelength of 215 nm. (Figure 1).

Linearity

Different solutions were injected into the system to obtain the AUC. The calibration graph was plotted for concentration against AUC, and the regression equation and coefficient were Y= 86.26 x + 24.55, 0.9999 for TEL; Y= 95.41 x + 10.59, 0.9999 for MET; and Y= 184.8 x + 95.01, 0.9999 for CLI. The data revealed the linearity of the method.

Precision

Intra-day and Inter-day studies were performed at different intervals, and the results obtained were 0.29% for TEL, 0.46% for MET, and 0.83% for CIL. All results were less than 2%, indicating the method's precision.

System suitability: All data were subjected to computing % RSD and were less than 2%. Therefore, this method can be repeated.

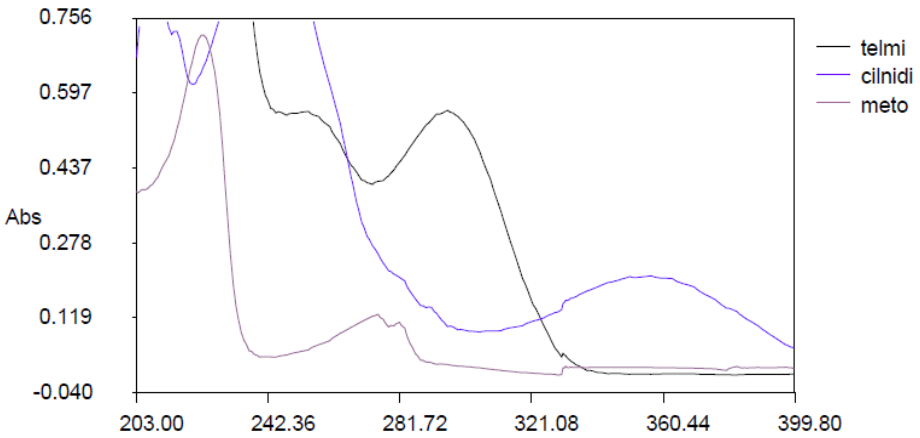

Figure 1. Selection of wavelength.

Accuracy: Recovery was obtained for TEL (98.59 – 101.57%), MET (98.32–101.53%), and CIL (99.15–101.76%). This demonstrates that the proposed method is accurate. (Table 1)

LOD and LOQ: The obtained values for TEL (1.26, 3.82), MET (0.46, 1.40), and CIL (0.69, 2.11) for LOD and LOQ, respectively, reflected that the method detected even minute amounts of drugs present in the solutions.

Robustness: Deliberate changes in various chromatographic parameters did not show any remarkable variation in the results. This indicates that the proposed method is robust.

Specificity: No interference was found from excipients or drugs during elution. This indicates that the proposed method is specific.

Degradation Study

The stability parameters were determined for the tablet dosage form. The TEL revealed that the percentages of acid degradation were 16.83%, 22.61%, 35.98%, 13.11%, and 25.59%, respectively. MET showed % degradation was 17.59%, 29.07%, 19.95%, 14.39%, 19.22% respectively. The % degradation for CIL was 23.80%, 36.67%, 16.25%, 17.53%, and 31.80%, respectively (Table 2). The oxidative degradation chromatogram is shown in Figure 2.

Table 1. Recovery study.

Concentration	TEL	MET	CLI
	% recovery		
80%	98.43	100.76	99.15
100%	100.88	98.32	100.34
120%	101.57	101.53	101.76

Table 2. Summary of degradation.

Condition	% degradation		
	TEL	***MET***	***CIL***
Acidic	16.83	17.59	23.80
Basic	22.61	29.07	36.67
Oxidation	35.98	19.95	16.25
Thermal	25.59	19.22	31.80
Photolytic	13.11	14.39	17.53

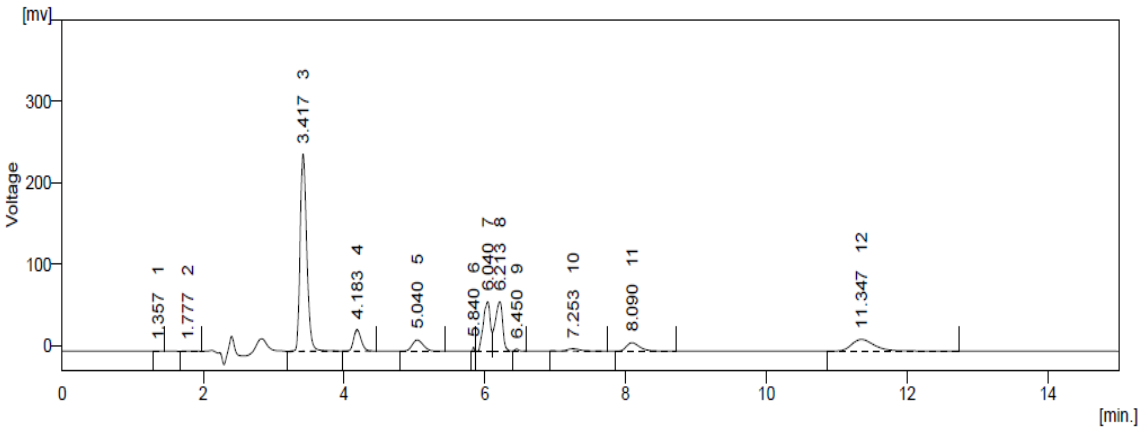

Figure 2. Oxidative degradation for TEL, MET, and CIL at 40 min.

Table 3. Summary of validation parameters.

Parameters	TEL	MET	CLI
Linearity (µg/ml)	2–6	2.5–7.5	0.5–1.5
Regression coefficient (R^2)	0.9997	0.9988	0.9989
Accuracy (%)	98.43–101.57	98.32–101.53	99.15–101.76
Intra-day precision (%RSD)	0.26%–0.29%,	0.33%–0.91%,	0.56%–0.83%
Inter-day precision (%RSD)	0.71%–0.94%	0.72%–0.94%	0.96%–1.90%
System suitability (%RSD)	0.84	0.87	0.50
LOD (µg/ml)	1.26	2.0	0.46
LOQ (µg/ml)	3.82	6.40	1.21
Robustness	Robust	Robust	Robust
Specificity	Specific	Specific	Specific

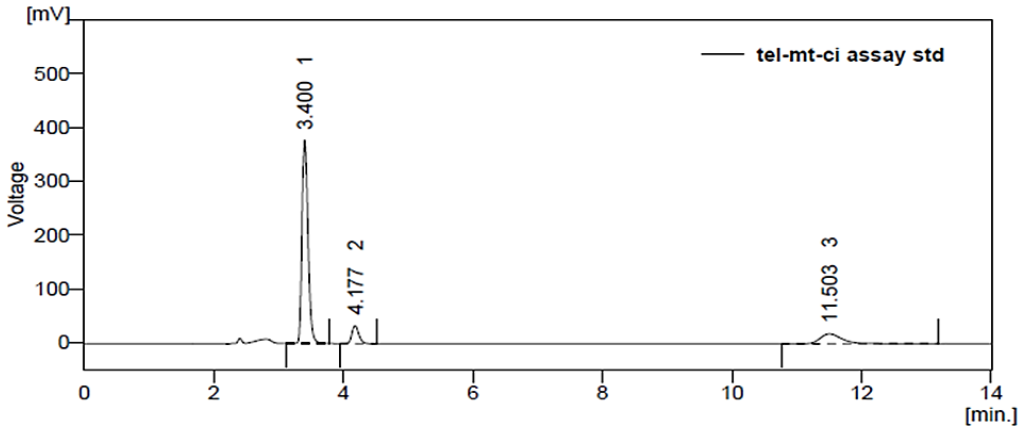

Figure 3. Chromatogram of TEL, MET, and CIL, at 3.4, 4.1, and 11.5 min., respectively.

CONCLUSION

Development and validation were conducted according to ICH guidelines. All the validation results and observations are depicted in Table 3. It has also been applied in marketed formulations. The chromatogram revealed the elution of all three drugs at 3.4, 4.1, and 11.5 min., for TEL, MET, and CIL, respectively (Figure 3). The results of the validation parameters demonstrated the accuracy, precision, repeatability, specificity, and sensitivity of the method. Therefore, the proposed method can be used for the routine simultaneous analysis of TEL, MET, and CLI in pharmaceutical preparations. In addition, the proposed method was applied to the degradation study. It was concluded that TEL was highly susceptible to oxidation, whereas MET and CIL showed more degradation under basic conditions. The drugs were least degraded under photolytic conditions. It has been observed that CIL showed remarkable degradation in comparison with TEL and MET.

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