INTERNATIONAL JOURNAL OF RESEARCH IN PHARMACY AND CHEMISTRY

Available online at www.ijrpc.com

*Research Article*

DOI: https://dx.doi.org/10.33289/IJRPC.12.4.2022.12(47)

# METHOD DEVELOPMENT AND VALIDATION FOR SIMULTANEOUS ESTIMATION OF TELMISARTAN AND ROSUVASTATIN IN BULK AND PHARMACEUTICAL DOSAGE FORMS BY RP-HPLC METHOD

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**ABSTRACT**

The main objective of the present work was to develop simple, precise, accurate and reproducible method development and validation for simultaneous estimation of Telmisartan and Rosuvastatin in Bulk and pharmaceutical dosage forms by RP-HPLC method. The separation of these two drugs using RP-HPLC was achieved on a SHISHEDO C18, 250×4.6mm, 5-micron size column with a mobile phase consisting Methanol and Phosphate Buffer PH-2.5 (70: 30% V/V) and flow rate of 1ml/min and UV detection at 245 nm. The retention times were observed to be 6.8 min and 8.8 min for Telmisartan and Rosuvastatin respectively. Linearity was found to be 40-120 µg/ml and 5-15 µg/ml for Telmisartan and Rosuvastatin respectively. The method was statistically validated for Linearity, Recovery, Limit of detection, Limit of quantification, Accuracy, Precision. The developed method was successfully validated for accuracy, precision, linearity, limit of detection, limit of quantification & robustness. Hence, this method can be used for simultaneous estimation of Telmisartan and Rosuvastatin in bulk and pharmaceutical dosage forms.

**Keywords:** Telmisartan and Rosuvastatin, UV-Spectrophotometry, RP-HPLC and ICH Guidelines.

## INTRODUCTION

### TELMISARTAN

IUPAC NAME 4-{[4-methyl-6-(1-methyl-2-benzimidazolyl)-2- propyl-1-benzimadazolyl] methyl-2-biphenyl carboxylic acid, Molecular Formula $C_{33}H_{30}N_4O_2$, Molecular Weight 514.61 g/mol, Appearance A white to off- white crystalline powder, Solubility: Soluble in Methanol, Acetonitrile, $P^{ka}$ 3.65, Melting point 261-263$^0$C, PHARMACOKINETIC DATA: Bioavailability 42-100 % , Protein binding 99 % , Highly bounds to plasma proteins Metabolism Minimal hepatic, Half life time Approximately 24hours, Excretion Faeces, Urine , Category Anti Hypertensive agent, Angiotensin-II receptor antagonist. Angiotensin-II receptor antagonist. Mode of action Angiotensins attachment to the receptors cause muscle cells to shorten and narrow the blood vessels (vasoconstrict), which leads to an increase in B.P (hypertension). Telmisartan blocks the angiotensin receptor by blocking the action of angiotensin. Telmisartan widens the blood vessels (vasodilate) and reduces blood pressure. Side effects Dizziness Blurred vision.

### ROSUVASTATIN

IUPAC NAME (3R,5S, 6E)-7-[4-(4-Fluorophenyl)-2-(N-methyl methane sulfonamide)-6-(propan-2-yl) pyrimidin-5-yl) 3,5dihydroxy hept-6-enoic acid. Molecular Formula $C_{22}H_{28}FN_3O_6S$, Molecular Weight 481.53 g/mol, Appearance A White or almost white, amorphous powder Solubility Soluble in Methanol, Water, Ethanol, $P^{ka}$4.0, Melting point151-156 °C PHARMACOKINETIC DATA: Bioavailability20%Protein binding88% Half life time19 hours Metabolism Not extensively metabolized Excretion Renal and Hepatic routes Category Anti Lipidemic agent. MODE OF ACTION: It is

competative inhibitor of HMG-COA reductase. This catalyses the conversion of HMG-COA to Mevalonate which is an early rate limiting step in cholesterol bio synthesis. The overall effect is decrease in plasma LDL and VLDL. Side effects: Kidney problems and Allergic reactions.

## MATERIALS AND METHODS

### MATERIALS USED

#### Chemicals and reagents used

Methanol and Acetonitrile of HPLC grade was supplied by Merck Limited, Mumbai. Water HPLC grade was supplied by Thermo fisher scientific India Pvt ltd, Mumbai. Working Standards of Telmisartan and Rosuvastatin were obtained from the Yarrow chemical works (P) ltd, Mumbai, Maharashtra, India.

#### Instruments used

i. Shimadzu single pan electronic balance(AX 200)
ii. Systronics - pH meter, μ pH system (7114).
iii. Shimadzu gradient HPLC system with following configurations
- LC-20 AD solvent delivery system (pump)
- SPD 20A UV Visible dual absorbance detector
- LAB Solutions data station
- Hamilton syringe
- Analytical column Shiseido $C_{18}$ (250 x 4.6 mm, 5μm)

iv. Labindia UV-VIS spectrophotometer
v. Loba life ultrasonicator (D10/IH)
vi. Fischer scientific filter paper 0.45 microns

#### Estimation of drugs

#### Optimization of chromatographic conditions for the estimation

Proper selection of the chromatographic method depends upon the nature of the sample (ionic or neutral molecule), its molecular weight and solubility. The drugs selected for the present study are polar in nature and hence either reverse phase or ion pair or ion exchange chromatography can be used. For the present study reverse phase HPLC method is considered to be more suitable because they are extremely specific, linear, precise, accurate, sensitive and rapid method.

#### Selection of detection wavelength for Telmisartan and Rosuvastatin

10 µg/ml solutions of Telmisartan and Rosuvastatin were prepared in Methanol. This solution was scanned in the UV region of 200 - 400 nm and the UV spectrum was recorded. From the spectra, detection wavelength 245 nm was selected.

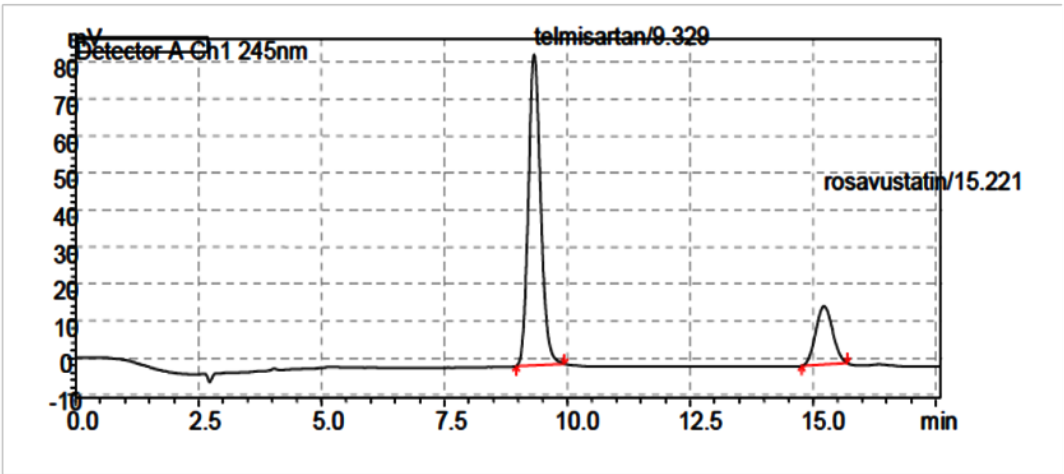


**Fig. 1: Typical chromatogram of Telmisartan and Rosuvastatin**

## OBSERVATION

The chromatogram observed that the retention time for Telmisartan is 9.3 mins and Rosuvastatin is 15.2 mins. The retention time is more when compared to 70:30 mobile phase retention times.

**Optimized chromatographic conditions**

The following chromatographic conditions were selected for the estimation of selected drugs in the marketed product. Stationary phase: Shiseido $C_{18}$(250 x 4.6 mm, 5μm), Mobile Phase:Methanol: Phosphate buffer pH 2.5 (70:30v/v), Flow rate:1 ml/min, Sample volume:20 μl, Detection:245 nm, Column temperature: Ambient, Run time:12 min.

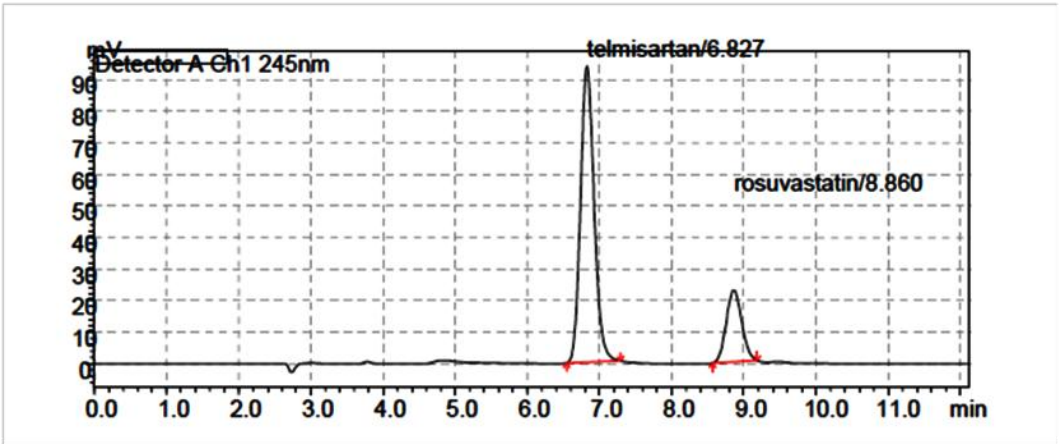


**Fig. 2: Combined chromatogram of Telmisartan and Rosuvastatin**

**OBSERVATION**

Good separation and resolution was observed with less retention time. Tailing was observed 1.0 and 1.1 within the limits. Theoretical plates were 6096 and 7464 and limit is more than 2000.And it was the final optimized trail. Retention time for the drugs was found to be 6.8 and 8.8 min for Telmisartan and Rosuvastatin respectively.

**Drug content**

The drug content in the formulations of Telmisartan and Rosuvastatin was estimated by aforesaid procedure. The retention times of Telmisartan and Rosuvastatin were 6.8 and 8.8 min, respectively.

**Preparation of standard and sample solutions**

**a. Standard stock solution of Telmisartan and Rosuvastatin**

10 mg of Telmisartan and Rosuvastatin working standards were accurately weighed and transferred into two 10 ml volumetric flasks and dissolved in Methanol and made up to the volume with the same solvent to produce 1mg/ml of Telmisartan and Rosuvastatin respectively. The stock solutions were stored in refrigerator at –20 ± $2^0$C until analysis.

The stock solutions were diluted to suitable concentrations with solution to obtain calibration curve (CC) standards and quality control (QC) samples.

**b. Calibration curve standards and quality control samples**

Working **solutions for calibration** and controls were prepared from the stock solutions by an adequate dilution using Methanol: Phosphate buffer pH 2.5 (70:30 v/v/). Calibration standards for control samples were prepared by diluting this stock solution to obtain the concentration levels of 10, 15, 20, 25 and 30 µg/ml for Telmisartan and 5, 7.5, 10, 12.5 and 15 µg/ml for Rosuvastatin respectively. Quality control samples were prepared as bulk, at a concentration of10 µg/ml(LQC), 20 µg/ml (MQC) and 30 µg/ml (HQC) for Telmisartan and 5 µg/ml (LQC), 10 µg/ml (MQC) and 15 µg/ml for Rosuvastatin respectively. These samples were stored below -50°C until use.

**RESULTS AND DISCUSSION**

**Validation of HPLC method**

Estimation of the drugs in marketed formulations was carried out using optimized chromatographic conditions. The validation parameters such as accuracy, precision (repeatability and reproducibility), linearity and range, sensitivity (limit of detection and limit of quantification), robustness/ruggedness, stability, selectivity/specificity and system suitability were evaluated.

**SPECIFICITY**

**Blank Interference**

A study to establish the interference of blank was conducted. Mobile phase was injected as per the test method. Chromatogram of blank should not show any peak at the retention time of analyte peak.

**SYSTEM SUITABILITY**

**Rosuvastatin and Telmisartan Identification**

Solutions of individual standard and combined samples were prepared as per the test procedure and injected into the HPLC system. There should not be any change in the retention times of the two drugs when injected individually and in combination.

**Acceptance Criterion**

Individual chromatograms of standard drugs and combined sample should be identical with near retention times.

**Table 1: System suitability studies**

| Sl.no | Parameters | Telmisartan | Rosuvastatin |
|---|---|---|---|
| 1 | Theoretical Plates | 7464 | 6096 |
| 2 | Resolution factor | 1.0 | 1.1 |
| 3 | LOD(µg/ml) | 0.1 | 0.1 |
| 4 | LOQ(µg/ml) | 0.3 | 0.8 |

**SENSITIVITY**

The limit of detection for Telmisartan and Rosuvastatin were found to be 0.1 mg/ml and 0.1 mg/ml respectively, limit of quantification for Telmisartan and Rosuvastatin were found to be 0.3 mg/ml and 0.8 mg/ml respectively.

**LINEARITY**

The linearity was plotted within the range of 5, 7.5, 10, 12.5 and 15 µg/ml for Rosuvastatin and 10, 15, 20, 25 and 30 µg/ml for Telmisartan.

**Table 2: Concentration-Peak Area for Rosuvastatin**

| Concentration (µg/ml) | Peak Area |
|---|---|
| 5 | 219522 |
| 7.5 | 322272 |
| 10 | 463309 |
| 12.5 | 564901 |
| 15 | 677948 |
| **Correlation coefficient** | **0.997** |

**Table 3: Concentration-Peak Area for Telmisartan**

| Concentration (µg/ml) | Peak Area |
|---|---|
| 10 | 819326 |
| 15 | 1213236 |
| 20 | 1639982 |
| 25 | 2047129 |
| 30 | 2499194 |
| **Correlation coefficient** | **0.999** |

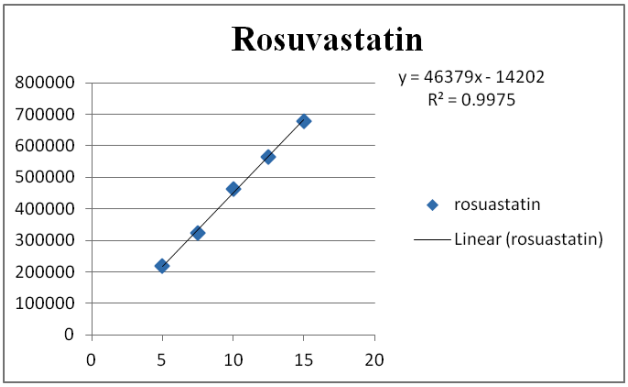


**Fig. 3: Graph showing Linearity of Rosuvastatin**

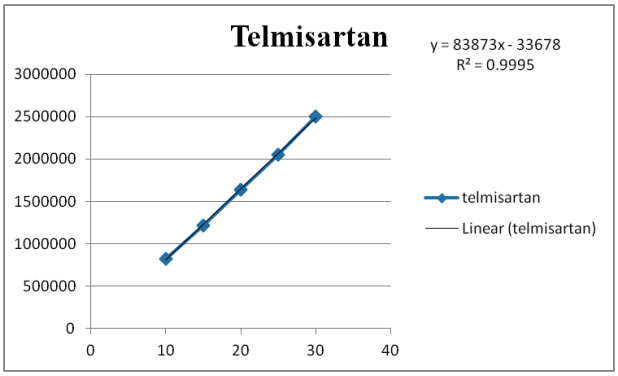


**Fig. 4: Graph showing Linearity of Telmisartan**

**Table 4: System precision study for Telmisartan and Rosuvastatin**

| S.No | Peak area of Telmisartan (20 µg/ml) | Peak area of Rosuvastatin (10 µg/ml) |
|---|---|---|
| 1 | 1229461 | 340250 |
| 2 | 1240793 | 344325 |
| 3 | 1233084 | 344090 |
| 4 | 1226759 | 344867 |
| 5 | 1235687 | 346758 |
| 6 | 1246685 | 334567 |
| **Mean** | **1235412** | **342450** |
| **S.D (+/-)** | **737.19** | **4434.03** |
| **C.V. (%)** | **0.59** | **1.29** |
| **N** | **6** | **6** |

**PRECISION**

The precision of the assay was measured by the percent coefficient of variation over the concentration range of low, middle and high quality control samples of Rosuvastatin and Telmisartan during the course of validation.

**Table 5: Method Precision study (Intraday) for Telmisartan and Rosuvastatin**

| S.No | Peak area of Telmisartan 20µg/ml | Peak area of Rosuvastatin 10µg/ml |
|---|---|---|
| 1 | 858383 | 211778 |
| 2 | 883434 | 20988 |
| 3 | 858798 | 203771 |
| 4 | 856754 | 205445 |
| 5 | 886753 | 205744 |
| 6 | 856544 | 213544 |
| **Mean** | **866777.7** | **208261.7** |
| **S.D (+/-)** | **14253.38** | **3892.54** |
| **C.V. (%)** | **1.644** | **1.869** |
| **N** | **6** | **6** |

**Table 6: Method Precision study (Interday) for Telmisartan and Rosuvastatin**

| S.No | Peak area of Telmisartan (20µg/ml) | Peak area of Rosuvastatin (10µg/ml) |
|---|---|---|
| 1 | 851282 | 207087 |
| 2 | 843434 | 206194 |
| 3 | 861129 | 205972 |
| 4 | 867645 | 201456 |
| 5 | 858931 | 201276 |
| 6 | 851614 | 208989 |
| **Mean** | **85567255** | **205162.3** |
| **S.D (+/-)** | **8593.728** | **3127.558** |
| **C.V. (%)** | **1.00** | **1.524** |
| **N** | **6** | **6** |

**ACCURACY (RECOVERY STUDY)**

Analyte recovery is a comparison of the analytical response from an amount of analyte added to quality control samples at three concentration levels.

**Table 7: Accuracy study for Telmisartan**

| Level | Concentration of sample(µg/ml) | Concentration of Standard(µg/ml) | Amount of drug recovered (µg/ml) | Recovery (%) |
|---|---|---|---|---|
| Level I | 10 | 10 | Mean:19.92<br>CV:0.175<br>N:3 | 99.6 |
| Level II | 20 | 10 | Mean:29.98<br>CV:0.034<br>N:3 | 99.9 |
| Level III | 30 | 10 | Mean:39.98<br>CV:0.076<br>N:3 | 99.9 |

**Table 8: Accuracy study for Rosuvastatin**

| Level | Concentration of sample(µg/ml) | Concentration of Standard(µg/ml) | Amount of drug recovered (µg/ml) | Recovery (%) |
|---|---|---|---|---|
| Level I | 5 | 10 | Mean:14.98<br>CV:0.057<br>N:3 | 99.8 |
| Level II | 10 | 10 | Mean:19.96<br>CV:0.076<br>N:3 | 99.8 |
| Level III | 15 | 10 | Mean:24.9<br>CV:0.166<br>N:3 | 99.9 |

**ROBUSTNESS**

Robustness of the method was studied by injecting the standard solutions with slight variations in the optimized conditions namely, ± 1% in the ratio of Acetonitrile in the mobile phase, varying pH range ±1 and ± 0.1 ml of the flow rate.

**Table 9: Robustness (change in flow rates) study for Rosuvastatin**

| S.no | Flow rate (ml/ min) | Retention time (min) | Peak Area | RSD (%) | System suitability results | |
|---|---|---|---|---|---|---|
| | | | | | Plate count | Tailing factor |
| 1 | Less Flow (0.9) | 9.4 | 479296<br>477635<br>476876 | 0.258 | 8194 | 1.07 |
| 2 | Actual Flow (1.0) | 8.8 | 479696<br>476086<br>473667 | 0.636 | 7123 | 1.07 |
| 3 | More Flow (1.1) | 7.8 | 475858<br>476766<br>478566 | 0.288 | 7091 | 1.07 |

**Table 10: Robustness (change in flow rates) study for Telmisartan**

| S.no | Flow rate (ml/ min) | Retention time (min) | Peak Area | RSD (%) | System suitability results | |
|---|---|---|---|---|---|---|
| | | | | | Plate count | Tailing factor |
| 1 | Less Flow (0.9) | 7.3 | 1789627<br>1765843<br>1757853 | 0.933 | 6563 | 1.112 |
| 2 | Actual Flow (1.0) | 6.8 | 1754394<br>1759849<br>1758958 | 0.166 | 6975 | 1.103 |
| 3 | More Flow (1.1) | 6.1 | 1775875 | 1.020 | 5639 | 1.100 |

**RUGGEDNESS**

Ruggedness of the method was studied by changing the experimental conditions such as operators, instruments, source of reagents, solvents and column of similar type.

**SUMMARY AND CONCLUSION**

The developed HPLC method allows rapid and precise determinations of Telmisartan and Rosuvastatin with an economical mobile phase. The scope of the present work is to expand the optimization of the chromatographic conditions and develop a sensitive RP-HPLC method using Phosphate buffer at pH 2.5 and Methanol (70:30 v/v) as an ideal mobile phase. Since it gives a good resolution and peak shapes with perfect optimization. The flow rate at 1 ml/min was optimized. A wavelength of 245 nm was selected as detection wavelength. The retention times were found to be 8.8 mins and 6.8 mins for Rosuvastatin and Telmisartan respectively. The limit of detection for Telmisartan and Rosuvastatin were found to be 0.1 & 0.1 µg/ml and the limit of quantification was found to be 0.3 & 0.8 µg/ml. The linearity and correlation coefficient ($R^2$) of Telmisartan and Rosuvastatin was found to be 10-30 µg/ml and 5-15 µg/ml respectively and $R^2$ value is 0.999 and 0.997 respectively. The percentage recoveries of Telmisartan and Rosuvastatin were found to be 99.9 % and 99.8 % respectively. Acceptance criteria according to ICH guidelines (98 to 102 %).The

isocratic elution technique developed for the determination of Telmisartan and Rosuvastatin ideally suited for rapid and routine analysis. This method shows good reproducibility of the results. Hence this method was simple, sensitive and accurate. Robustness for the developed method was carried out and the results were observed to be within the limits. From the above experimental data results, it was concluded that the developed RP - HPLC method has the following advantages. The standard and sample preparations requires less time. No tedious extraction procedures was involved in the analytical process. Hence, the chromatographic method developed for Telmisartan and Rosuvastatin was found to be simple, precise, accurate, sensitive, faster elution and cost effective. The developed RP-HPLC method is an alternative one for the reporting methods which varies the parameters of mobile phase, column, detection wave length, LOD, LOQ, run time when compared to developed alternative method. The results of analysis have been validated as per ICH guidelines.

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