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Simultaneous Estimation of Rosuvastatin Calcium and Ezetimibe in Bulk and Tablet Dosage Form by Simultaneous Equation Method

Chirag B. Pandya*, K. P. Channabasavaraj, Shridhara H S

Department of Pharmaceutical Analysis, Bharathi College of Pharmacy, Bharathinagara, Maddur, Karnataka-571422, India.

Corres.author: chirag_pandya44@yahoo.com
Mob: 09742445869

Abstract : Rosuvastatin Calcium and Ezetimibe in combination are available as tablet dosage forms in the ratio of 1 : 1. A simple, sensitive, accurate and reproducible method have been developed for simultaneous estimation of both the drugs by the Simultaneous equation method, using methanol as solvent. Rosuvastatin Calcium has absorbance maxima at 243.60 nm and Ezetimibe at 232.60 nm and both shows linearity in the concentration range of 5-40 µg/ml. The limit of detection were found to be 1.5 µg/ml and 1.65 µg/ml for Rosuvastatin Calcium and Ezetimibe respectively. The limit of quantification for Rosuvastatin Calcium and ezetimibe were found to be 4.5 µg/ml and 4.96 µg/ml respectively. The Results were found to satisfactory and reproducible. The said method was validated according to ICH guidelines. Recovery study was performed to confirm the accuracy of the method.
Key words: Rosuvastatin Calcium, Ezetimibe, Simultaneous estimation, Validation.

1. INTRODUCTION:

Rosuvastatin Calcium[1] is official in indian pharmacopoeia. It is chemically (*E*)-(3*R*,5*S*)-7-{4-(4-fluorophenyl)-6-isopropyl-2-{methyl(methylsulphonyl amino)]pyrimidin-5-yl}-3,5-dihydroxyhepten-6-oic acid calcium. It is used as a lipid lowering agent act by inhibition of 3-hydroxy-3-methylglutaryl-coenzymeA (HMG-CoA) reductase. Rosuvastatin is orally administered as calcium salt. Ezetimibe[9], (3*R*,4*S*)-1-(4-flourophenyl)-3-[(3*S*)-3-(4-flourophenyl)-3-hydoxypropyl]-4-(4-hydroxypenyl)azetidine-2-one, is an anti-hyperlipidemic medication, acts by decreasing cholesterol absorption in the intestine. Both drugs are used in combination to treat dyslipidemia, hyperlipidemia, hypercholesterolemia and to prevent cardiovascular disease including atherosclerosis.

Numbers of reported method were already available for the individual determination of both drugs.
Rosuvastatin calcium alone has been determined by Spectrophotometric methods[2][3][4], Stability indicating method[5], HPTLC[5] and RP-.HPLC.[6][7][8] Ezetimibe was also estimated using UV- method[10][11][12], Derivative Spectroscopy[13][14], HPLC[15][16], HPTLC[17] and LC-MS/MS[18]. To the best of knowledge, only two methods has been developed for the simultaneous determination of both the drugs in tablets include Q ratio and first derivative methods[19]. The present research work describes the rapid, accurate, sensitive and reproducible spectroscopic method for simultaneous estimation of Rosuvastatin Calcium and Ezetimibe from the tablet formulation.

2. EXPERIMENTAL

2.1 Instruments and reagents

A Shimadzu UV - 1800 UV/VIS spectrophotometer was used with 1 cm matched quartz cell.

All the chemicals used were of analytical grade. Methanol A.R. grade was procured from Loba Chem. Ltd., Mumbai. An analytically pure sample of Rosuvastatin Calcium and Ezetimibe were procured as gift sample from Zydus-Cadila Pharmaceuticals Ltd.(Ahmedabad, India) and Watson Pharma. (Mumbai, India) respectively. Tablet formulation[ROZAVEL-EZ Sun Pharmaceuticals Ltd, Silvassa, India] was procured from a local pharmacy with labeled claim 10 mg each of Rosuvastatin Calcium and Ezetimibe per tablet.

2.2 Preparation of standard stock solution

Stock solutions of both the drugs were prepared by dissolving accurately weighed 100 mg of each standard drugs in 100 ml methanol. Both stock solution (100 µg/ml) were further diluted to produce solutions of 15 µg/ml and scanned in the entire UV range (200 - 400 nm) to determine the absorbance maxima.

Absorbance maxima of Rosuvastatin Calcium and Ezetimibe were detected at 243.60 nm (λ_2) and 232.60 nm (λ_1), respectively. Both the spectras were overlained. Both the drugs showed linearity with absorbance in the range 5-40 µg/ml, when measured at 232.60 nm and 243.60 nm. Calibration curves were plotted from the absorbance values at these wavelengths.

2.3 Analysis of marketed formulations

Twenty tablets of formulation were accurately weighed and powdered. An amount of powder equivalent to 10 mg of both the drugs was weighed and dissolved in 100 ml of methanol. It was filtered through Whatman filter paper No. 41 after subjecting 30 minutes for sonicating and then final dilution was made with methanol to get final concentration.

2.4 Simultaneous equations method

The developed method was based on simultaneous equations method. Absorbance maxima of Rosuvastatin Calcium and Ezetimibe were 243.60 nm (λ_2) and 232.60 nm (λ_1), respectively. Calibration curve for Rosuvastatin Calcium and Ezetimibe was prepared in the concentration rang 5-40 µg/ml. The absorptivity coefficients of the two drugs were determined by using Beer's law. The overlain spectra of Rosuvastatin Calcium and Ezetimibe are represented in [Figure - 1]. A set of two simultaneous equations was developed using these absorptivity coefficients. These are: A_1 =0.0400 Cx+0.0466Cy…(1); and A_2 =0.0468 Cx+0.0346 Cy…(2), where A_1 and A_2 are absorbances at 232.60 nm and 243.60 nm respectively, and Cx and Cy are concentrations of for Ezetimibe and Rosuvastatin Calcium respectively.

FIGURE-1:

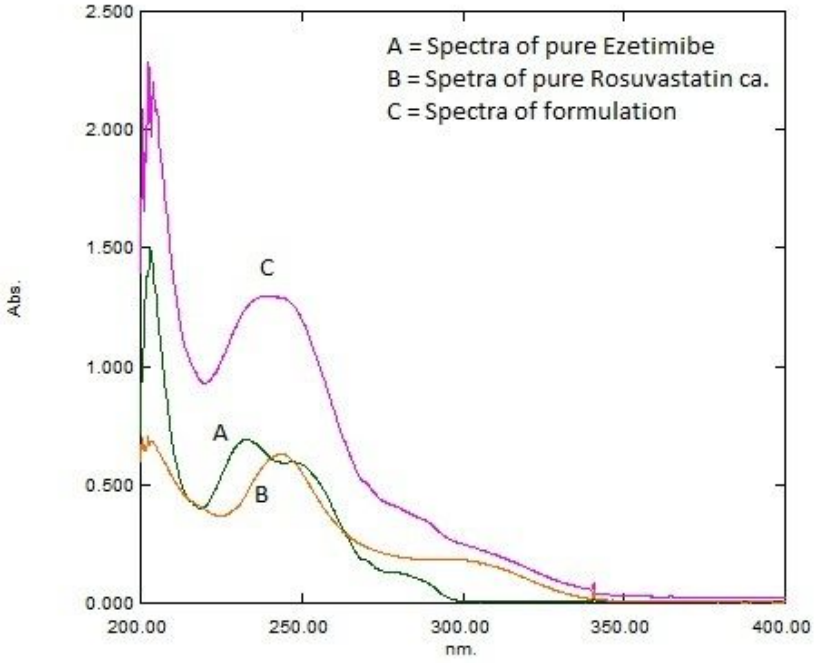

Table No. 1 : Calibration parameters

Sr. No.	Parameter	Rosuvastatin Calcium	Ezetimibe
1	Absorption Maxima (nm)	243.60	232.60
2	Beer's Law limits(mg/ml)	5-40	5-40
3	Regression equation (y)* Slope (b) Intercept (a)	 0.0583 0.0265	 0.0483 0.0242
4	Correlation coefficient	0.9979	0.9992
5	Limit of detection (µg / ml)	1.5	1.65
6	Limit of quantification (µg / ml)	4.5	4.96

*y = a ± bx; where x is the concentration in mg/ml and y is absorbance.

Table No 2: Results of Recovery study.

Drugs	Excess Drug added (µg / ml)	Amount recovered* (µg / ml)	% Recovery	% RSD
Rosuvastatin Calcium	8	7.94 ± 0.04	99.25	0.041
	10	10.05 ± 0.07	100.50	0.074
	12	12.07 ± 0.10	100.58	0.103
Ezetimibe	8	7.93 ± 0.04	99.13	0.04
	10	9.94 ± 0.03	99.40	0.029
	12	12.03 ± 0.06	100.25	0.063

* is average of six determinations.

Table No 3: Result of Intra-Day and Inter-Day Precision

Drug	Concentration (µg /ml)	Intra-day Amount Found*	% RSD	Inter-day Amount Found*	% RSD
Rosuvastatin Calcium	15	99.89 ± 0.82	0.818	99.93 ± 0.61	0.613
Ezetimibe	15	100.02 ± 0.48	0.484	99.84 ± 0.53	0.529

* is average of six determinations.

Table No 4: Assay results of Ezetimibe and Rosuvastatin Calcium in tablet.

Drugs	Amount (mg / Tablet)		% Lable claim (%Found ± SD)*
	Labeled (mg)	Found (Mean ± SD)	
Rosuvastatin Calcium	10 mg	9.96 ± 0.05	99.6 ± 0.96
Ezetimibe	10 mg	9.98 ± 0.14	99.8 ± 1.05

* is average of six determinations.

3. RESULT AND DISCUSSION

The method was validated according to International Conference on Harmonization guidelines. Linear regression equations (intercepts and slopes) for mixtures of Rosuvastatin Calcium and Ezetimibe were established. The high values of the correlation coefficients and the values of *Y*-intercepts close to zero indicate the good linearity of the calibrations. The values of slope, intercept and correlation coefficient values are given in Table 1. Limit of detection and limit of quantitation were determined by using the formula based on the standard deviation of response and the slope. The limit of detection and limit of quantification were calculated by using the equation LOD = 3.3 x σ / S and LOQ = 10 x σ / S, where σ is the standard deviation of intercept, S is the slope and it is mentioned in Table 1.

To study the accuracy of the developed method, and to check the interference of excipients used in the dosage forms, recovery studies were carried out by the standard addition method and results are shown in Table 2. Precision method was studied as intra-day and

inter-day variations. Results for precision study are reported in Table 3. The results of analysis of marketed formulation are shown in Table 4. The values obtained are within the limit.

4. CONCLUSION

The developed method was found to be simple, sensitive, accurate and reproducible and can be used for routine quality control analysis of Rosuvastatin Calcium and Ezetimibe in bulk and in pharmaceutical formulations.

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