International Journal of Research in Pharmacy and Pharmaceutical Sciences
ISSN: 2455-698X
Impact Factor: RJIF 5.22
www.pharmacyjournal.in
Volume 3; Issue 1; January 2018; Page No. 71-78

A review on chromatographic and spectrophotometric method for estimation of Rosuvastatin calcium and Gemigliptin in synthetic mixture

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Abstract
Gemigliptin is a dpp-4 inhibitor which is use for type 2 diabetes. DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn increases insulin secretion and decreases blood glucose level. Rosuvastatin is a HMG-CoA inhibitor, it reduce the cholesterol level. Fixed dose Combination of Gemigliptin and Rosuvastatin showed significant improvement in HbA1C and LDL-C level in T2DM patient with Dyslipidemia and the therapy was well tolerated.

Keywords: gemigliptin, rosuvastatin, UV-Spectroscopy, HPLC (high performance liquid chromatography), HPTLC (high performance thin layer chromatography), LC (liquid chromatography)

Introduction [1-5, 43]

Gemigliptin is a class of oral antidiabetic which is used to control glucose level in the people with type 2 diabetes mellitus. It is an oral anti-hyperglycemic agent to optimized DPP-4 inhibitor. It helps to prevent kidney injury and it is used to increase insulin level and reduce the glucagon level, decrease fasting and postprandial glycemia. Gemigliptin inhibites the glucose lowering effects of Dipeptidyl peptidase-4 the enzyme which is responsible for inactivation of incretin hormones GLP-1 and GLP (gastric inhibitory polypeptide). The mechanism of DPP-4 inhibitors is to increase incretin levels (GLP-1 and GIP), which inhibit glucagon release, which in turn decreases gastric emptying, and decreases blood glucose levels.

Rosuvastatin is an indicated class of statin and inhibitor of the enzyme HMG-CoA reductase. It is used for the treatment of dyslipidemia, Hypercholesterolemia, triglycemia. It works by three mechanism 1) Inhibiting cholesterol synthesis, 2) Increasing LDL uptake, 3) Decreasing of specific protein prenylation. They are used to treatment of Dyslipidemia. Controlling high cholesterol helps in prevention of primary cardiovascular function (event) relative risk of heart attack and stroke in patients.

The combination of Gemigliptin and rosuvastatin shows well tolerated and significant improvement in the Type 2 diabetes patients having Dyslipidemia. Gemigliptin and rosuvastatin fixed dose combination showed significant improvement in HbA1C and LDL-C level in T2DM patient with Dyslipidemia and the therapy was well tolerated. In the clinical trial the patient with Dyslipidemia who could not achieve adequate glycemic control with stable monotherapy of Metformin where given fixed dose combination of Gemigliptin and Rosuvastatin in the dose of 50mg and 20mg.

Reported methods are categorized depending on the following considerations:

1. Single component analyzed by UV spectroscopy method and chromatographic method.
2. Analysis of Gemigliptin and Rosuvastatin combination with other drug UV- Spectrophotometric method and Chromatographic method.

Literature Review of Rosuvastatin Calcium [6-7]

Table 1: Official method for estimation of Rosuvastatin calcium

Sr. No	Drug	Method	Description
1	Rosuvastatin calcium API (IP 2014)	Liquid Chromatography	Detection Wavelength: 248 nm Mobile Phase: 0.2% acetic acid in water: acetonitrile: methanol: (50:2:25:25 v/v/v/v) Stationary Phase: Stainless steel column (25 cm × 4.6 mm) packed with octadeylilane bonded porous silica (5µm) Flow Rate: 1 ml/min Injection Volume: 20 µl
2	Rosuvastatin Tablet (IP 2014)	Liquid Chromatography	Detection Wavelength: 248 nm Mobile Phase: mixture of buffer solution prepared by dissolving ammonium acetate in 900mL water adjust pH 4.0 with glacial acetic acid and dilute to 1000 ml: acetonitrile: tetrahydrofurane:(585/360/50 v/v/v) Stationary Phase: Stainless steel column (25 cm × 4.6 mm) packed with octadeylilane bonded

			porous silica (5µm) Flow Rate: 1.5 ml/min Injection Volume: 20 µl
3	Rosuvastatin calcium API (EP 2013)	Liquid Chromatography	Detection Wavelength: 242 nm Mobile Phase: Mobile phase A: 1%v/v solution of trifluoroacetic acid R: acetonitrile: water :(1:29:70 v/v/v) Mobile phase B: 1% v/v solution of trifluoroaceti acid R: water: acetonitrile (1:24:75 v/v/v) Stationary Phase: octadecylsilyl silica gel Flow Rate: 0.75 ml/min Injection Volume:10 µl

1.2 Reported Methods for Estimation of Rosuvastatin Calcium [8-39]

Table 2: Reported Method of Rosuvastatin Calcium

Sr. No.	Drug	Method	Description
1.	Rosuvastatin in Pure form and marketed formulation	UV- Spectrophotometer	Detection Wavelength: 225 nm Solvent: Methanol Linearity Range: 5-35 µg/ml Correlation coefficient: 0.982
2.	Aspirin and rosuvastatin in combination dosage form	Derivative Spectrophotometry	Detection Wavelength: Rosuvastatin: 255 nm Aspirin: 288.50 nm Linearity Range: Rosuvastatin: 4-28 µg/mL Aspirin: 20-140 µg/mL Limit of Detection: Rosuvastatin: 0.205µg/mL Aspirin: 1.234 µg/mL Limit of Quantitation: Rosuvastatin: 0.622 µg/mL Aspirin: 3.740 µg/mL
3.	Rosuvastatin in bulk and tablet dosage form	UV- Spectroscopy	Detection wavelength: 234.60-251.00 nm. Solvent : Methanol Linearity range: 2-12 µg/ml Limit of detection: 0.1581 µg/ml Limit of Quantitation: 0.4792µg/ml
4.	Rosuvastatin Calcium in bulk	UV- Spectroscopy	Detection wavelength: 422.7 nm Linearity range: 99.2-101.6 µg/ml
5.	Rosuvastatin Calcium and Fenofibrate in Tablet	Derivative spectrometric	Detection wavelength: Rosuvastatin: 243nm Fenofibrate: 224nm Linearity range : Rosuvastatin: 4-12 µg/mL Fenofibrate: 16-48 µg/mL Correlation coefficient: Rosuvastatin: 0.9963 Fenofibrate: 0.996 Limit of detection: Rosuvastatin: 1.96 µg/mL Fenofibrate: 0.76 µg/mL Limit of Quantitation : Rosuvastatin: 5.96 µg/Ml Fenofibrate: 2.32 µg/Ml
6.	Rosuvastatin and Ezetimibe from their combination tablet dosage form	RP-HPLC	Detection wavelength: 230 nm Mobile phase: Acetonitrile: water: 0.02 M phosphate buffer pH 8 (40:10:50 v/v) Stationary phase: C18 250 × 4.6 mm, 5µ column Flow rate: 1.0 ml/min Linearity range: 30–90 µg /mL Limit of detection: Rosuvastatin: 0.05 µg/ml Ezetimibe: 0.006 µg/ml Limit of Quantitation: Rosuvastatin: 0.08 µg/ml Ezetimibe: 0.05 µg/ml
7.	Rosuvastatin calcium and propranolol hydrochloride in bulk drug and pharmaceutical dosage	UV-Spectrophotometric	Detection wavelength: Propranolol hydrochloride: 289 nm Rosuvastatin: 243nm Linearity range:

	form		Propranolol hydrochloride: 2 – 42 µg/Ml Rosuvastatin: 2–40 µg/mL Correlation coefficient : Propranolol hydrochloride: 0.9984 Rosuvastatin: 0.9996 Limit of detection: Propranolol hydrochloride: 0.3279 µg/mL Rosuvastatin: 0.1961 µg/mL Limit of Quantitation: Propranolol hydrochloride: 0.9937 µg/mL Rosuvastatin: 0.5944 µg/Ml
8.	Rosuvastatin and Amilodipin in pharmaceutical formulation	HPLC	Detection Wavelength: 240nm Mobile phase: Acetonitrile:0.1M Ammonium acetate buffer (30:70v/v) Flow rate: 1.5ml/min Linearity range : Rosuvastatin: 1-200 µg/ml Amlodipine: 0.5-100 µg/ml Correlation coefficient: Rosuvastatin: 0.996 Amlodipine: 0.994 Limit of detection: Rosuvastatin: 0.30 µg/ml, 0.15 µg/ml Amlodipine: 0.5 µg/ml,1 µg/ml
9.	Rosuvastatin and Fenofibrate in Bulk Drug	UV – Spectrophotometric	Detection Limit: Rosuvastatin: 244 nm Fenofibrate: 286 nm Solvent: methanol Linearity Range: Rosuvastatin: 1-10µg/ml Fenofibrat: 2-20µg/ml Correlation co-efficient: Rosuvastatin: 0.0998 Fenofibrate: 0.999
10.	Rosuvastatin and Ezitimibe in pharmaceutical formulation	Liquid chromatography	Detection Wavelength: 254 nm Mobile Phase: sodium acetate buffer: acetonitrile (30:70v/v) Flow Rate: 1.2ml/min Linearity and range: 0.5-250 µg/ml Detector: photo diode array detector Correlation coefficient: Rosuvastatin: 0.993 Ezitimibe: 0.996
11	Rosuvastatin calcium and Amlodipine besylate in tablet formulation	RP-HPLC	Detection wavelength: 242 nm Mobile phase: acetonitrile: potassium dihydrogen phosphate buffer(diluted with ortho poshoric acid):(45:55v/v) Retention time: Rosuvastatin calcium: 4.42min Amlodipine besylate: 2.91min
12.	Rosuvastatin calcium and aspirin in bulk and pharmaceutical dosage form	UV-spectrophotometric	Detection wavelength: 244 nm Linearity range: Rosuvastatin calcium: 10-50 µg/ml Aspirin: 40-120 µg/ml Limit of detection: Rosuvastatin calcium:1.6730 µg/ml Aspirin: 7.4278 µg/ml Limit of Quantitation: Rosuvastatin calcium: 5.0696 µg/ml Aspirin: 22.5083 µg/ml
13	Rosuvastatin calcium and Ezitimibe in bulk and tablet dosage form	UV- spectrophotometric	Detection wavelength: 243.60 nm and 232.60 nm Linearity range: 5-40 µg/ml Limit of detection: Rosuvastatin calcium: 1.5 µg/ml Ezitimibe: 1.65 µg/ml Limit of Quantitation: Rosuvastatin calcium: 4.5 µg/ml Ezitimibe: 4.96 µg/ml
14.	Rosuvastatin calcium in pure and tablet dosage form	Stability indicating - HPLC	Detection wavelength: 245 nm Mobile phase: Sodium hydrogen phosphate: acetonitrile: (50/50 v/v) Correlation coefficient: 0.9995 Limit of detection:1.50 µg/ml

			Limit of Quantitation:4.56 µg/ml
15.	Rosuvastatin calcium in bulk and tablet dosage form	RP-HPLC	Detection wavelength: 243 nm Mobile phase: acetonitrile: phosphate buffer:(60/40 v/v) Linearity range: 20-60 µg/ml
16.	Rosuvastatin calcium in marketed formulation	UV-Spectrophometric	Detection Wavelength: 252 nm Linearity range: 5-35 µg/ml
17.	Rosuvastatin in Nano formulation and pharmaceutical dosage form	RP-HPLC	Detection wavelength: 241nm Mobile phase: Buffer: acetonitrile:(50/50 v/v) Limit of detection: 0.17 µg/ml Limit of Quantitation: 0.7 µg/ml Correlation coefficient: 0.9998
18.	Rosuvastatin calcium in pharmaceutical dosage forms	Extractive spectrophometric (ion-pair complex)	Detection Wavelength: 518 nm Linearity rage: 5-25 µg/ml Limit of detection: 1.5 µg/ml Limit of Quantitation: 2.5 µg/ml Correlation coefficient: 0.9997
19.	Rosuvastatin and related substances in pharmaceutical dosage form	RP-UPLC	Detection wavelength: 240 nm Mobile phase: Triflouroacetic acid: Methanol Run time: 10 min Limit of detection: 0.079 µg/ml Limit of Quantitation: 0.075 µg/ml
20.	Rosuvastatin and Ezetimibe in human plasma	RP-HPLC	Detection Wavelength: 240 nm Mobile phase: phosphoric acid: acetonitrile (30:70 v/v) Stationary phase: C18 column Detector: photo diode arry detector Linearity range: Rosuvastatin: 0.32 mg/ml Ezetimibe: 0.08-67 mg/ml Correlation coefficient: Rosuvastatin: 0.9997 Ezetimibe: 0.9967 Limit of detection: Rosuvastatin: 0.106 µg/ml Ezetimibe: 0.026 µg/ml Limit of Quantitation: Rosuvastatin: 0.32 mg/ml Ezetimibe: 0.08 mg/ml
21.	Aspirin and rosuvastatin calcium in capsules	RP-HPLC coupled with photo diode array detection	Mobile phase: 20mm KH2PO4: methanol (30:70 v/v) Stationary phase: Merck hibar 250-4.6 RP18(5 µg) column (150mm×3.0mm) Linearity range: Aspirin: 15-90 µg/ml Rosuvastatin: 2-12 µg/ml Detector: Shimadzu SPD 20A detector Injection volume: 20 µl Retention time: Aspirin: 3.747min Rosuvastatin: 5.969 min Lowest limit of detection: Aspirin: 0.01535 ppm Rosuvastatin: 0.1358 ppm Lowest limit of Quantitation: Aspirin: 0.3097 ppm Rosuvastatin: 0.1063 ppm
22.	Rosuvastatin calcium and its lactone impurity in drug substance pharmaceutical dosage form	RP-HPLC	Detection Wavelength: 242 nm Solvent: Solvent A: (10 mm ammonium acetate) Solvent B: (acetonitrile: Methanol(50/50 v/v)) Stationary phase: Sunfire column C18(250×4.6 mm, 5 µm) Injection volume: 10 µl Retention time: 15 min Limit of detection: Lactone impurity: 0.01 µg/ml Limit of Quantitation: 0.04 µg/ml
23.	Rosuvastatin and Ezetimibe in combined tablet dosage form	RP-HPLC	Detection wavelength: 230 nm Mobile phase: Ammonium acetate in water as buffer, pH adjusted to 6.50±0.05 with dilute formic acid solution, acetonitrile (55:45 v/v) Stationary phase: Sunfire BDS C18 250X4.6 mm ID, 5 µm column

			Flow rate: 0.8 ml/min Linearity range: ;.Rosuvastatin: 98.19-294.56 µg /mL Ezetimibe: 99.12-297.36 Limit of detection: Rosuvastatin: 3.30 µg/ml Ezetimibe: 3.71 µg/ml Limit of Quantitation: Rosuvastatin: 10 µg/ml Ezetimibe: 11.24 µg/ml
24.	Rosuvastatin calcium in tablet	UV-Spectrophotometric	Detection wavelength: 243 nm Solvent: methanol Linearity range: 1-60 µg/ml Limit of detection: 0.33 µg/ml
25.	Rosuvastatin calcium and tablet	RP-HPLC	Detection wavelength: 242 nm Mobile phase: acetonitrile: water (40:60 v/v) Stationary phase: YMC C8, 150×4.6 mm i.d., 5 µm Detector: Photo diode array detector Retention time: 5.2 min Correlation coefficient: 0.9993 Limit of detection: 0.1 µg/ml Limit of quantitation: 0.5 µg/ml
26.	Rosuvastatin and Fenofibrate in Tablet Dosage form	RP-HPLC	Detection of wavelength: Rosuvastatin: 248 nm Fenofibrate: 286 nm Mobile phase: Water (pH adjusted to 2.5 with ortho phosphoric acid) and acetonitrile in ratio (30:70 v/v) flow rate: 1.0ml/min Stationary phase: (Inertsil ODS, 250 x 4.6mm, 5µ column) analytical column. retention time: Rosuvastatin: 3.6 min Fenofibrate: 20.5 min
27.	Rosuvastatin and Fenofibrate in Bulk And Pharmaceutical Dosage form	RP-HPLC	Detection of wavelength: 252 nm Mobile phase: acetonitrile: methanol: water (40:40: 20) Stationary Phase: C18 column (Agilent ODS UG 5 COLUMN 250X4.5mm Dimensions) Retention times: Rosuvastatin: 2.3 min Fenofibrate: 5.0 min Linearity range: Rosuvastatin: 1-5µg/ml Fenofibrate: 8-40µg/ml correlation coefficient: Rosuvastatin: 0.99968 Fenofibrate: 0.999691
28.	Rosuvastatin calcium in pure form and in Pharmceutical formulation	UV Spctrophotometer	Detection wavelength: 244 nm Linearity range: 2-18µg/ml
29	Rosuvastatin and Ezetimibe in pharmaceutical formulations	RP-HPLC	Detection wavelength: 298 nm Mobile phase: Ammonium Dihydrogen Phosphate (pH 3) Buffer solution: Methanol (65:35v/v, pH 3.0) Stationary phase: Inertsil ODS 3V C18 (250 x 4.6 mm, 5 µm) column Flow rate: 1.5 ml/min Retention time: Rosuvastatin: 6.1 min Ezetimibe: 16.2 min Linearity range: Rosuvastatin: 6-18 µg /mL Ezetimibe: 24-72 µg /mL Limit of detection: Rosuvastatin: 0.6 µg /mL Ezetimibe:2.4 µg /mL Limit of Quantitation: Rosuvastatin: 1.8 µg / Ezetimibe: 7.2 µg /mL
30	Rosuvastatin API	RP-HPLC	Detection wavelength: 254 nm Mobile phase: Ethanol:methanol:ethyl acetate (6:3:1 v/v) Stationary phase: NUCLEODUR 150 mm×4.6 mm RP C8 column Flow rate: 1.0 ml/min

31	Rosuvastatin calcium in bulk and pharmaceutical formulation	RP-HPLC	Detection wavelength: 242 nm Mobile phase: n-heptane, 2-propanol and trifluoroaceticacid (85:15:01v/v) Stationary phase: CHIRALPAK IB (250 x 4.6mm, 5µm) column Linearity range: 5-40 µg /mL Limit of detection: 0.07 µg/ml Limit of Quantitation: 0.2 µg/ml
32	Rosuvastatin calcium and Hydrochlorthiazide in their combined dosage forms	UV- Spectroscopy	Detection Wavelength: Rosuvastatin calcium: 243 nm Hydrochlorthiazide: 270 nm Linearity range: Rosuvastatin calcium: 5-15 µg/ml Hydrochlorthiazide: 6.25-18.75 µg/ml

2.1 Literature Review of Gemigliptin [40-42]

Table 3: Reported Method of Gemigliptin

Sr. No.	Drug	Method	Description
1	Gemigliptin API	**Stability indicating RP-HPLC**	Detection Wavelength:280 nm Solvent: Methanol Mobile phase: Acetonitrile: methanol: water (40:40:20 % v/v) Stationary phase: shimadzu LC-2010 Sheisdo C18 (250*4.6mm, 5µm) Flow rate: 1.0 ml/min Linearity Range: 50-300 µg/ml Injection volume: 10µm
2	Gemigliptin API	**LC-MS**	Solvent: Methanol Mobile phase: 0.1% formic acid in 10 mm ammonium acetate in water: Acetonitrile (10:90 % v/v) Stationary phase: Phenomenex Gemini C18 (3 µm, 30.0×20.0 mm) Linearity Range: 1ng/ml-2000 ng/ml Flow rate: 0.5 ml/min Injection volume: 2 µl
3	Gemigliptin and Metformin simultaneous estimation in bulk and pharmaceutical dosage form	**RP-HPLC**	Detection Wavelength: 260 nm Mobile phase: Methanol: phosphate buffer (70:30 % v/v) Stationary phase: Inertsil C18 column (4.6×150 mm, 5 mm) Linearity Range: metformin: 100-500 µg/ml Gemigliptin: 1-5 µg/ml Flow rate: 0.8 mL/min Correlation coefficient: 0.999

Conclusion

This review portray the reported Spectroscopic and Chromatographic methods developed and validated for estimation of Rosuvastatin calcium and Gemigliptin. According to this review it was concluded that for Rosuvastatin calcium and Gemigliptin different Spectroscopic and Chromatographic methods are available for single and combination. The mobile phase containing Phosphate buffer, Methanol and Acetonitrile were common for most of the chromatographic method to provide more resolution. For chromatographic method flow rate is observed in the range 0.5 -1.5 ml/min to get good resolution time. For most of the Spectroscopic methods common solvent is Phosphate buffer and Methanol. Hence this all methods found to be simple, accurate, economic, precise and reproducible in nature. Most of Methods were of RP-HPLC and UV absorbance detection because these methods provided with best available reliability, repeatability, analysis time and sensitivity.

Financial support and sponsorship: nil.

Acknowledgement

The authors are thankful to DR. K. Pundarikakshudu, Director of L.J. Institute of Pharmacy, Ahmedabad, India for providing all the facilities and encouragement to carry out work.

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