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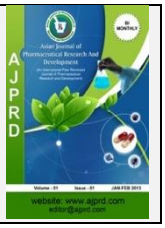

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Review Article

A Review on the HPLC Method Development and Validation Studies of Combined Dosage Form of Rosuvastatin and Ezetimibe

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A B S T R A C T

Analytical method development is an important aspect of drug development and manufacturing. An exceptional analytical method is the one which detects the active pharmaceutical ingredients as well as the impurities and other chemical entities which invariably enters the formulations due to various reasons. The methods which are developed accordingly are to be validated as per the ICH guidelines so as to be accepted in a commercial setting. Coronary Artery Disease is a life threatening condition, which affects millions of people, where the blood flow to the heart is affected due to plaque deposits. Patients are administered with combined dosages of Rosuvastatin and Ezetimibe for the effective treatment and management of the disease. Various pharmaceutical formulations are available with the combined dosage forms and analytical method development is necessary during the development of the drug so as to detect impurities and ascertain safety and efficacy. HPLC is the most effective and reliable methodology for the analysis of the pharmaceutical drug dosages which are released to the market by pharmaceutical companies. The review focus on the various methodologies developed over the years to effectively analyse the combined drug formulations of Rosuvastatin and Ezetimibe as per the ICH guidelines.

Keywords: Method Development, HPLC, Rosuvastatin, Ezetimibe, Combined dosage.

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INTRODUCTION:

Coronary Artery Disease (CAD) is a prevalent and potentially life-threatening condition that affects millions of people worldwide. The occurrence of the disease has alarmingly increased during the recent times, either due to changing food habits or constantly changing work scenario where physical activity has considerably reduced. It is one of the most common type of heart disease and occurs when the blood vessels supplying the heart muscle become narrowed or blocked by a buildup of fatty deposits, cholesterol, and other substances collectively known as plaque. Early detection and effective management significantly improve the prognosis of CAD. With lifestyle modifications and proper medical interventions, individuals can lead satisfying lives despite the presence of the disease.

Since the introduction of lovastatin (statins), the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have proved to be extremely effective in the management of coronary artery disease. These class of drugs are observed to reduce the low-density lipoprotein cholesterol without compromising safety thereby bringing necessary pharmacological effect. Therefore, Statin medications are widely prescribed to lower cholesterol levels in the bloodstream, primarily low-density lipoprotein (LDL) cholesterol. These drugs play a pivotal role in preventing and managing cardiovascular diseases, particularly Coronary Artery Disease (CAD). Statin class of molecular systems (atorvastatin, fluvastatin, lovastatin, pitavastatin, pravastatin, rosuvastatin, simvastatin etc.) represent a cornerstone in the prevention and management of cardiovascular diseases, offering an effectivemethodology to reduce cholesterol levels and mitigate the risk of heart-related events [1].

Rosuvastatin is recognized for its high potency in lowering LDL cholesterol levels. Clinical studies have demonstrated that Rosuvastatin not only lowers cholesterol but also plays a vital role in reducing the risk of cardiovascular events. Rosuvastatin provides incredible support in the management of cholesterol and cardiovascular health. Its effectiveness in

lowering cholesterol, together with its proven cardiovascular benefits, underscores its significance in preventing and treating atherosclerotic diseases. Rosuvastatin act as 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase inhibitors that are effective in the reduction of total and LDL cholesterol, by interfering with the cholesterol metabolic pathway involving mevalonic acid [2]. It is particularly effective at reducing the levels of very-low-density lipoprotein (VLDL) cholesterol, a key player in the development of atherosclerosis. Additionally, Rosuvastatin has been shown to increase high-density lipoprotein (HDL) cholesterol, the "good" cholesterol that helps remove LDL cholesterol from the bloodstream.

Ezetimibe is often used in combination with statins, providing a synergistic effect in lowering LDL cholesterol levels. Ezetimibe is a medication that plays a unique role in the management of cholesterol levels, particularly low-density lipoprotein (LDL) cholesterol. Unlike statins, which primarily act in the liver by inhibiting cholesterol synthesis, Ezetimibe works in the small intestine. It inhibits the intestinal absorption of dietary and biliary cholesterol thereby providing a synergy with the action of statin class of medications, without affecting the absorption of fat-soluble nutrients [3]. It selectively inhibits the absorption of cholesterol, including dietary cholesterol and cholesterol released from bile during digestion. By blocking this absorption, Ezetimibe further reduces the amount of cholesterol that enters the bloodstream enhancing the overall effective management of cholesterol levels. Therefore, Rosuvastatin and Ezetimibe combination is used together with a proper diet to lower bad cholesterol (LDL) in the blood. It is also used alone or together with other medicines to treat homozygous familial hypercholesterolemia (HoFH).

Rosuvastatin is chemically designated as (3R, 5S, 6E)-7-[4-(4-fluorophenyl)-2-(N- methyl methane sulfo namido) - 6 - (propan - 2 - yl) pyrimidin - 5 - yl] - 3, 5 - dihydroxyhept - 6 - enoic acid with empirical formula $C_{22}H_{28}FN_3O_6S$ and molar mass of 481.54 g/mol (Figure 1) It is a member of the drug class of statins. It is used in the treatment of Hyperlipidemia. Rosuvastatin Calcium (calcium salt) is a selective and competitive inhibitor of hydroxyl methyl glutaryl coenzyme A (HMG CoA) reductase (a precursor of cholesterol), the rate-limiting enzyme that converts 3-hydroxyl-3-methylglutaryl coenzyme A to mevalonate. It reduces levels of low-density lipoprotein, apolipoprotein B and triglycerides in the blood, while increasing levels of high-density lipoprotein in the management of hyper lipidaemias.

Ezetimibe,1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone has the empirical formula $C_{24}H_{21}F_2NO_3$ and a molar mass of 409.4 g/mol (Figure-2). Ezetimibe is highly soluble in alcohol (ethanol), methanol and acetone, but practically insoluble in water. After oral administration, Ezetimibe is rapidly and extensively metabolised to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide) in humans and animal species [3, 4].

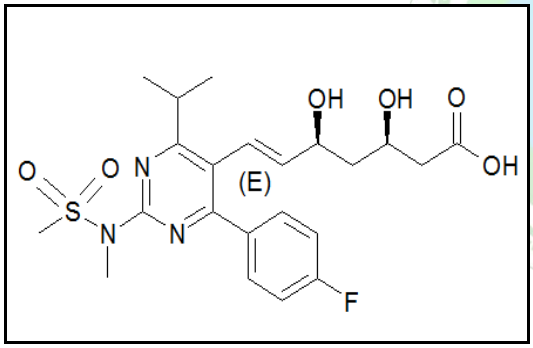

Figure-1: Molecular structure of Rosuvastatin

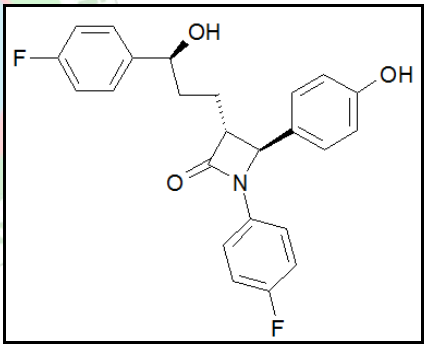

Figure-2: Molecular structure of Ezetimibe

The combination of Rosuvastatin and Ezetimibe is an effective treatment and management of hypercholesteremia as Rosuvastatin alone has relatively low efficacy in reducing other lipid fractions and achieve the low cholesterol goal. The combination drug, Rosuvastatin calcium and Ezetimibe is available as tablet form and analysis of the combination drug is necessary. Literature survey reveals that various HPLC, LCMS and spectrophotometric methods have been reported for the determination of both Rosuvastatin and Ezetimibe in pure and pharmaceutical formulations as combined dosages. Various other methods such as capillary zone electrophoresis, spectrofluorometric, HPTLC etc. have been reported for the determination of the combined drugformulations also [5]. However, the HPLC methods remains as the most reliable and undisputed analytical tool for the assay of pharmaceutical drug formulations with utmost assay accuracies.

Analysis of active pharmaceutical ingredients and excipients in a formulation and pure drug during the manufacturing process is a key aspect in pharmaceutical drug development. The method should ideally detect all the possible chemical entities that may be present due to various factors of manufacturing process, storage and stress, apart from the assay of active molecule, is an important aspect of analytical method. The presence of chemical entities other than active ingredient and excipients may compromise the safety and efficacy of a drug formulation. A very effective HPLC method could detect the presence of all the chemical entities present in a formulation.Therefore, understanding of various methodologies is essential in analytical method development to arrive on a most suitable method so as to serve the purpose of the analytical problem in hand. The present review focuses on the HPLC methods which are available for the analysis of Rosuvastatin and Ezetimibe as combined drug formulation which has been recorded in various literatures. All the methods presented has followed the ICH guidelines in developing the methodologies [6, 7].

A simple, precise and rapid stability-indicating reversed-phase high performance liquid chromatographic (RP-HPLC) method

was developed by Gajjar et al. The ICH validated method deals with the simultaneous determination of Rosuvastatin and Ezetimibe from their drug combination. The method used Hypersil C18 150 x 4.6 mm, 5µ column. The mobile phase consisted of 0.05 M phosphate buffer (pH 2.5)-methanol (45+55, v/v), with a flow rate of 1.0 ml per min at 40^{o}C under UV detector set at 252 nm. The stress study was conducted for the combination drug on thermal, photolytic, hydrolytic and oxidative stress conditions and the method offered distinct peak separations. Linearity was obtained in the concentration range of 5-80 µg/mLfor both drugs with correlation coefficients of 0.99999 and 0.99994 respectively. Mean percent recovery of triplicate samples at each level for both drugs were found in the range of 98% to 102% [8].

Varghese and Ravi developed an isocratic method for the simultaneous determination of tablet combination form on HPLC. The method used Chromolith C18 column (100 x 6 mm id) using 0.1% (v/v) orthophosphoric acid solution (pH 3.5)-acetonitrile (63 + 37, v/v) mobile phase at a flow rate of 1 mL/min at ambient temperature. The method used DAD detector at 245 nm wave length with total elution time of 20 minutes. The method was evaluated as per the ICG guidelines which showed the desired linearity and other recommended parameters with recovery of 98.37-100.13 % for Rosuvastatin and 99.75-101.0% for Ezetimibe [9].

In another study, a simple, rapid, economic, sensitive and precise HPLC method has been developed for the simultaneous determination of Rosuvastatin and Ezetimibe in pharmaceutical dosage form. The method was developed on Sunfire BDS C18 (250 X 4.6 mm, 5 µm) column on a flow rate of 0.8 mL/min with ammonium acetate in water as buffer, pH adjusted to 6.50±0.05 with dilute formic acid solution, acetonitrile in proportion of ratio 55:45 v/v. The UV detection method was employed with detector set to 230 nm wavelength. The retention time of Rosuvastatin and Ezetimibe were 2.74 and 4.80 respectively with the ICH mandated analytical parameters. Linearity of Rosuvastatin and Ezetimibe were in the range of 98.19 to 294.56 µg/mL and 99.12 to 297.36 µg/mL respectively. The percentage recoveries of both the drugs were 99.9% and 100.9% for Rosuvastatin and Ezetimibe respectively from the tablet formulation. The proposed method is suitable for the routine quality control analysis of simultaneous determination of Rosuvastatin and Ezetimibe in bulk and pharmaceutical dosage form [10].

Another stability indicating reverse phase liquid chromatographic method was developed for the simultaneous determination of Rosuvastatin and Ezetimibe in pharmaceutical formulations by SPK Bandaruetal. The validated method used reverse phase elution method with C18 column (250 X 4.6 mm, 5µm) with photo diode array (PDA) detector. The method achieved the desirable linearity under the isocratic conditions with sodium acetate buffer (pH 4.0) and acetonitrile (30:70, %v/v) combination mobile phase with a flow rate of 1.2 mL/min and the detector set at 254 nm. The method shows linearity over a concentration range of 0.5–250 µg/ml for both Rosuvastatin and Ezetimibe. The method achieved short elution times at 2.563 min for Rosuvastatin and 3.629 min for Ezetimibe with recovery of 98.29-101.48 % and 99.41-99.81 % for both drugs respectively [11].

Rajashekaretal. developed a simple and validated reversed phase high performance liquid chromatographic method for the simultaneous determination of Rosuvastatin and Ezetimibe in pharmaceutical tablet dosage form. The method used Symmetry X-terra C8 (4.6mm x 100mm, 5 µm) column at ambient temperature with a mixture of ortho phosphoric acid buffer and acetonitrile in the ratio 40:60 v/v as mobile phase. The flow rate was maintained at 1.0 mL per min at 237 nm detector setting showing the analytes, Rosuvastatin and Ezetimibe being eluted at 2.490 and 3.173 min, respectively. The method exhibited an accuracy of 99.59% to 100.70% for both the analyte molecules. Calibration plots obtained were linear over the concentration ranges 10–50 µg/mL for both pharmaceutical ingredients. The validated method as per ICH guidelines showed linearity in the concentration range of 10-50 µg ml-1 and 10-50 µg/mL with recoveries observed at 98.84 to 100.00% for Rosuvastatin and 100.02 to 101.5% for Ezetimibe [12].

In another study by Rao et. al., a rapid, sensitive, specific and simultaneous reverse phase high performance liquid chromatographic method was developed and validated for Rosuvastatin Calcium and Ezetimibe in a combined dosage form. The method employed Enable C18G (5 micron, 250 mm x 4.6 mm i. d.) column with acetonitrile-water (75:25 v/v) mobile phase flowing at a rate of 0.6 ml/min. and the UV detector set to 252 nm. The peaks were observed at 2.931 mins for Rosuvaststin and at 6.531 mins for Ezetimibe. The linearity and range for both Rosuvastatin Calcium and Ezetimibe were 5-40 µg/ml and 5-40 µg/ml, respectively. The recovery studies showed 99.6-100.3 % for Rosuvastatin Calcium and 99.5-99.9% for Ezetimibe with a precision of <2% [13].

In another method development study, a simple, specific, accurate and precise RP-HPLC method was developed and validated for the simultaneous estimation of Rosuvastatin Calcium and Ezetimibe in pharmaceutical formulation with forced degradation studies. The method was developed using Enable C 18G column (250 ×4.6 mm, 0.5 µm) with mobile phase consisted of acetonitrile and 1 % acetic acid in water at the ratio of 80:20 %v/v with a flow rate of 1 mL/min .UV detection was carried out at 252 nm. The retention time for Rosuvastatin Calcium and Ezetimibe were found to be 2.928 and 6.553 min respectively. The proposed method was validated for linearity, range, accuracy, precision, robustness, LOD and LOQ. Linearity was observed over a concentration range 0.5-250 µg/ml for Rosuvastatin Calcium and 0.5-250 µg/ml for Ezetimibe. The % RSD for Intraday and Interday precision was found to be 0.56 and 0.36 for Rosuvastatin Calcium and 0.50 and 0.32 for Ezetimibe. The LOD and LOQ were found to be 0.04 µg/ml and 0.16 µg/ml for Rosuvastatin Calcium and LOD and LOQ were found to be 0.03 and 0.11 µg/ml for Ezetimibe respectively. Rosuvastatin Calcium and Ezetimibe were subjected to stress conditions of degradation including acidic, alkaline, oxidative, thermal and photolysis. The percent recovery of Ezetimibe and Rosuvastatin Calcium was found to be 99.86-100.33 % and 99.63100.19% [14].

Ramachandran et. al. developed an ICH guideline-based RP-HPLC method for the determination of Rosuvastatin and Ezetimibe in tablet dosage form. The method was based on isocratic elution method on a mobile phase consisting of acid

buffer, acetonitrile and methanol consisting of a composition of 40:30:30 v/v. The method was executed on a Hypersil ODS column (4.6 x 250 mm, 5 µm) and flow rate of 1.5 ml/min where Rosuvastatin and Ezetimibe were eluted with a retention time difference of 2 min, which was detected on a UV detector placed at 230 nm. The method established appreciable linearity and recovery, which was tested positively for the other parameters under ICH guideline. The method showed linearity for Rosuvastatin as 11-33 µg/ml and Ezetimibe as 10-30 µg/ml with 99.6-101.1% and 99.9-100.7% respectively as recovery [15].

Deshpande et. al. developed a simple, rapid, specific and sensitive reverse phase high performance liquid chromatography for the simultaneous estimation of Rosuvastatin calcium and Ezetimibe in combined tablet formulation. The method used HiQSil C18 column (4.6mm x 250 mm, 5µm) with a mobile phase consisting of acetonitrile: water (80: 20 v/v) at a flow rate of 1.0 mL min-1. The analytes were eluted at a flow rate of 1.0 ml/min to be detected at a wavelength of 241 nm. Under this condition, Rosuvastatin Calcium showed the retention time of 1.758 min and Ezetimibe, 3.133 min. The method was validated as per the ICH guidelines and found to be linear at the concentration range of 5-30 µg/mL for both the drugs. The mean percentage recovery was found to be 99.85-100.84 and 99.99 to 101.20 for Rosuvastatin calcium and Ezetimibe, respectively. The method was found to be rugged and robust for the quantification of both the drugs in its dosage form and bulk drug [16].

Patel et. al. has developed another ICH guided methodology for the estimation of Rosuvastatin and Ezetimibe. The developed method on RP-HPLC was validated for the estimation of Rosuvastatin and Ezetimibe in capsule dosage form. The methodology used Inertsil ODS3 (100 mm x 4.6 mm i.d, 3 µm) column with mobile phase consisting of disodium hydrogen phosphate dihydrate buffer solution with pH adjusted to 5.0 with dilute phosphoric acid and acetonitrile (60:40 %v/v) with a flow rate of 1.5 ml/min. The detector was set at 232 nm. The retention time were observed at 3.03 min for Rosuvastatin and 11.89 min for ezetimibe. The method offered linearity over the concentration range 5.0-20 µg/ml for both Rosuvastatin and Ezetimibe. The method exhibited excellent sensitivity with LOD and LOQ values of 0.0282 µg/ml and 0.0853 µg/ml for Rosuvastatin and 0.0297 µg/ml and 0.0901 µg/ml for Ezetimibe. The recovery was recorded for Rosuvastatin between 99.3 – 101.9% and for Ezetimibe between 103 – 103.6%. The study also covered the forced degradation process under acidic, alkaline, oxidation, humidity and thermal degradation. The method was simple, specific, precise, robust and accurate for estimation of Rosuvastatin and Ezetimibe in capsule dosage form [17].

Kurbanogluet. al. developed another method on HPLC for the assay analysis of Rosuvastatin and Ezetimibe tablet form. The method was dependent on Zorbax SB-C18 (100 mm x 4.6 mm, 3.5 µm) column with mobile phase consisting of water containing 0.1% H_3PO_4:methanol:acetonitrile (50:25:25 v/v/v) kept on a flow rate of 1.2 ml per minute. The method used UV detector with the wavelength set at 242 nm. This simultaneous method was further employed on degradation studies, obtaining exceptional sensitivity and selectivity with required linearity response, LOD and LOQ parameters. The method showed linear relationships varying from 0.05 to 50 µg/mL for Ezetimibe concentrations and from 0.05 to 25 µg/mL for Rosuvastatin concentrations respectively [18].

CONCLUSION:

Perusing through the literatures, it is evident that the analytical method has been developed in reverse phase which is ideal for both the molecular systems. Both the molecular structures are highly polar in nature and therefore the reverse phase mode will help to develop method which provides earlier elution of the active molecules. Entry numbers 4 and 7 (Table-1) provides exceptional linearity range for both the active ingredients. The method also provides early elution of Rosuvastatin and Ezetimibe within the duration of 6.5 minutes which reduces the overall run time, making suitable for commercial labs and manufacturing facilities. The other studies mentioned in the review will provide more insights for the development of suitable methods for various laboratories engaged in the analysis of Rosuvastatin and Ezetimibe pharmaceutical ingredients as individual or combined formulations according to their needs. The concise of the methods which has been discussed earlier is given in Table-1.

Table-1: A concise of the analytical parameters of the methods discussed

Sr No	Column	Detector	Mobile phase	Retention time (in minutes)	Linearity range	Recovery
1	Hypersil C18 150 x 4.6 mm, 5µ column	UV 252 nm	Phosphate-methanol, pH 2.5	Rosuvastatin -5.54 Ezetimibe -13.25	5-80 µg/ mL	Rosuvastatin - 98% to 102% Ezetimibe - 98% to 102%
2	Chromolith C18 column	PDA 245 nm	0.1% (v/v) orthophosphoric acid solution (pH 3.5)-acetonitrile (63 + 37, v/v)	Rosuvastatin – 4.8 Ezetimibe -10.9	0.5 to 10.0 µg /mL	Rosuvastatin – 98.37-100.13 % Ezetimibe – 99.75-101.0%
3	Sunfire BDS C18 (250 X 4.6 mm, 5 µm)	PDA 230 nm	Ammonium acetate in water as buffer, pH adjusted to 6.50±0.05 & acetonitrile (ratio 55:45 v/v)	Rosuvastatin - 2.74 Ezetimibe – 4.80	Rosuvastatin - 98.19 to 294.56 µg/mL Ezetimibe - 99.12 to 297.36 µg/mL	Rosuvastatin – 99.9 to 100.9% Ezetimibe – 99.9 to 100.9%
4	C18 (250 mm × 4.6 mm i.d., 5 µm particle size)	PDA 254 nm	Sodium acetate buffer (pH 4.0) and acetonitrile (30:70, %v/v)	Rosuvastatin-2.563 Ezetimibe-3.629	0.5–250 µg/ml	Rosuvastatin - 98.29-101.48 % Ezetimibe - 99.41-99.81 %

5	Symmetry X-terra C8 (4.6mm x 100mm, 5 µm)	UV 237 nm	Ortho phosphoric acid buffer and acetonitrile in the ratio 40:60 v/v	Rosuvastatin- 2.490 Ezetimibe – 3.173	10–50 µg mL-1	Rosuvastatin - 98.84 to 100.00% Ezetimibe - 100.02 to 101.5%
6	Enable C18G (5 micron, 250 mm x 4.6 mm i. d.)	UV 237 nm	Acetonitrile-water (75:25 v/v)	Rosuvastatin-2.931 Ezetimibe- 6.531	5-40 µg/ml	Rosuvastatin - 99.6-100.3 % Ezetimibe - 99.5-99.9%
7	Enable C 18G column (250 ×4.6 mm, 0.5 µm)	UV 252 nm	Acetonitrile and 1 % acetic acid in water at the ratio of 80:20 %v/v	Rosuvastatin - 2.928 Ezetimibe - 6.553 min	0.5-250 µg/ml	Rosuvastatin - 99.86-100.33 % Ezetimibe – 99.63100.19%.
8	Hypersil ODS column (250 x 4.6 mm, 5µ)	UV 252 nm	Acetic acid, acetonitrile, methanol (40:30:30)	Rosuvastatin -3.7 Ezetimibe – 5.7	10-30µg/ml	Rosuvastatin - 99.6-101.1% Ezetimibe - 99.9-100.7%
9	HiQSil C18 column (4.6mm x 250 mm, 5µm)	UV 230 nm	Acetonitrile: Water (80: 20 v/v)	Rosuvastatin - 1.758 Ezetimibe – 3.133	5-30 µg/ mL	Rosuvastatin - 99.85-100.84% Ezetimibe – 99.99 to 101.20%
10	Inertsil ODS3 (100 mm x 4.6 mm i.d, 3 µm)	UV 232 nm	Disodium hydrogen phosphate dihydrate buffer solution with pH adjusted to 5.0 with dilute phosphoric acid and acetonitrile (60:40 %v/v)	Rosuvastatin - 3.03 Ezetimibe – 11.89	5.0-20 µg/ml	Rosuvastatin – 99.3 – 101.9% Ezetimibe – 103 – 103.6%
11	Zorbax SB-C18 (100 mm x 4.6 mm, 3.5 µm)	UV 242 nm	water containing 1% H3PO4:methanol:acetonitrile (50:25:25 v/v/v)	Rosuvastatin – 2.80 Ezetimibe – 4.50	Rosuvastatin - 0.05 to 25 µg/mL Ezetimibe – 0.05 to 50 µg/mL	Rosuvastatin – 100.80 Ezetimibe – 101.0

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