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Spectrophotometric first order derivative method for simultaneous determination of Rosuvastatin and Fimsartan in Synthetic mixture

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Abstract
A simple, economical, accurate, precise and less time-consuming Spectrophotometric first order derivative method for simultaneous estimation of Rosuvastatin and Fimasartan in synthetic mixture. In this method Rosuvastatin and Fimasartan are exhibits maximum absorbance (λ max) at 263 nm and 246 nm with methanol as the solvent. The method was validated as per the ICHQ2R1 guidelines. Drugs followed the linearity in the concentration range of 30-150 µg/mL and 5-30 µg/Ml for Rosuvastatin and Fimasartan respectively. The validity of the proposed method was assessed by applying the standard addition technique where the % recovery of the added standard was found to be 99.79 and 98.96 for Rosuvastatin and Fimasartan. The proposed method is recommended for routine analysis of ROS and FIM in synthetic mixture in regular quality control testing laboratories.

Keywords: Rosuvastatin, fimasartan, UV spectrophotometry, beer's law, validation

Introduction
Hypertension is a sustained increase in blood pressure ≥ 140/90 mm Hg, a indicator where the risk of hypertension-related cardiovascular disorder is more enough to merit medical observation [1]. Rosuvastatin calcium (ROS) which chemically known as (3R, 5S, 6E)-7-(4-(4-fluorophenyl)-6-(1-methylethyl)-2-(ethyl(methylsulfonyl)amino)-5-pyrimidinyl)-3, 5 dihydroxy-6-heptenoic acid. Fimasartan potassium trihydrate which is chemically known as 2-(2-butyl-4-methyl-6-oxo-1-{[2′-(1H-1,2,3,4tetrazol-5-yl)-[1,1′-biphenyl]-4-yl] methyl }-1, 6-dihydropyrimidin-5-yl)-N, N dimethylethanethioamide. Rosuvastatin calcium is an HMG Co A reductase inhibitor and Fimasartan is an angiotensin II receptor antagonist [2, 3]. Rosuvastatin and Fimasartan used in combination to treat hypertension [4-5]. The mechanism of action of rosuvastatin is blocking 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase [6]. This enzyme is the rate-limiting step in cholesterol synthesis and decreases the production of mevalonic acid from HMG-CoA. Moreover, this results in a rise of low-density lipoprotein receptors on hepatocyte membranes and stimulation of low-density lipoprotein catabolism. HMG-CoA reductase inhibitors also decrease levels of high sensitivity C-reactive protein (CRP). They also have pleiotropic properties, involving inhibition of platelet aggregation, anticoagulant effects, reduced inflammation at the site of a coronary plaque, and enhanced endothelial function [7]. In blocking the AT1 receptor, fimasartan blocks vasoconstriction and supports vasodilation. At the kidney and adrenal gland, AT1 blockage and inhibition of aldosterone formation rise the excretion of water and salt by the kidneys, which lowers overall blood volume [8]. At the heart, AT1 blockage lowers contractility and the stimulatory effects of the sympathetic nervous system [9]. Generally, fimasartain helps to a decrease in blood pressure and relieves hypertensive symptoms. ARBs such as fimasartan have also been shown to be protective against stroke, myocardial infarction, and heart failure [10].
Literature survey reveals that Rosuvastatin can be estimated by spectrophotometric, Reverse Phase High Performance Liquid Chromatography (RP-HPLC) and High Performance Thin Layer Chromatography (HPTLC) methods either as a single or in combination with other drugs in pharmaceutical preparations.

Analytical methods reported for Fimasartan includes spectrophotometric HPLC and HPTLC either as a single drug or in combination with other drugs. Literature survey reveals that not a single UV method of analysis has yet been reported for simultaneous analysis of Rosuvastatin and Fimasartan. The objective of the present investigations was to develop a rapid, accurate, economical and validated First order derivative Ultra-Violet spectrophotometric (UV) method for the simultaneous estimation so that can play important role in quantification of ROS and FIM in synthetic mixture [11-20].

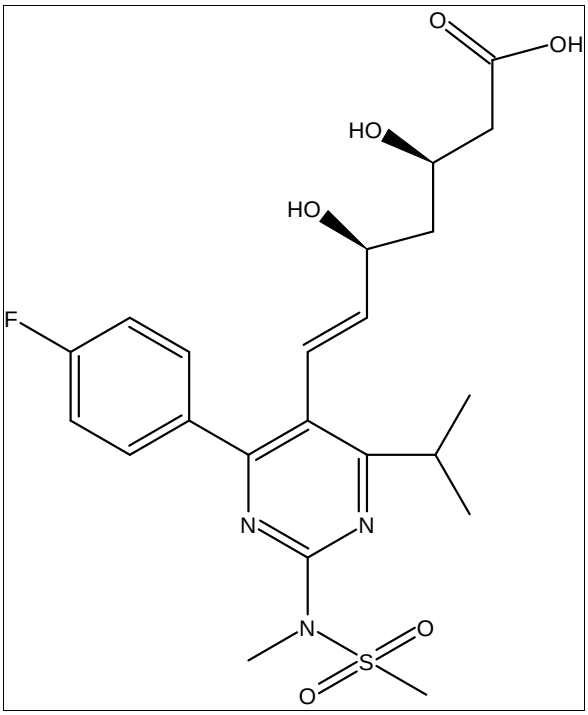

Fig 1: Chemical structure of Rosuvastatin

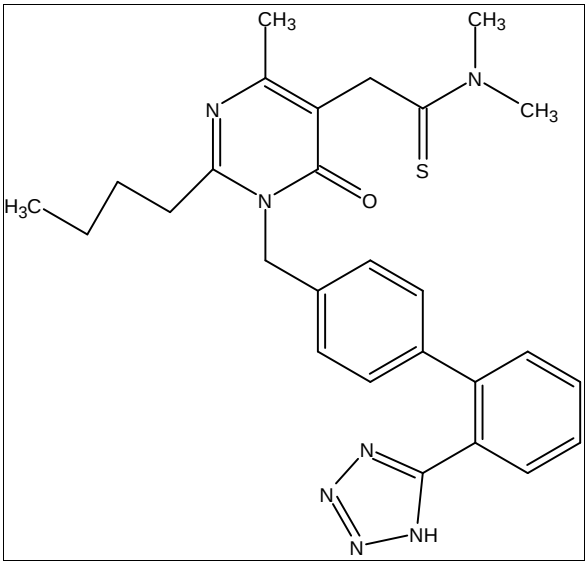

Fig 2: Structure of Fimasartan

Materials and Methods

Instrumentation

The instrument used in the present study was UV-Visible spectrophotometer (Lab India-UV 3000+) with spectral band width of 1 nm. All weighing was done on electronic balance (Model Shimadzu AUX-220).

Chemicals and Materials

Pharmaceutical grade of Rosuvastatin (ROS) and Fimasartan (FIM) were kindly supplied as a gratis sample by Montage Laboratories Pvt Ltd and Mackur Laboratories. In the present study the UV spectra of ROS and FIM were obtained from different solutions (Methanol, Acetonitrile, Distilled water) were studied. The two drugs were freely soluble in Methanol. At the end of these studies, Methanol was chosen as solvent for studied drugs.

Standard stock solutions

Standard stock solutions of ROS (100 µg/ml), FIM (600 µg/ml) were prepared in methanol. For the selection of analytical wavelength solutions of ROS (10µg/ml), FIM (60µg/ml) were prepared separately by appropriate dilution of standard stock solution with methanol and scanned in the spectrum mode from 200 to 400 nm.

Selection of wavelength

Standard solutions of both drugs (10 µg/ml and 60 µg/ml) were scanned separately in the range of 200- 400 nm. These spectrums were converted to first order derivative spectra by using derivative mode. For this method, 263 nm and 246 nm were selected as wavelengths of measurements for ROS and FIM respectively. There was proportionate increase in amplitude at 263 nm and 246 nm ROS and FIM respectively (Figure 3).

Linearity

The work in standard solutions were obtained by dilution of the stock solution in methanol. Series of solutions with concentration of 5-30 µg/ml and 30-150 µg/ml of ROS and FIM respectively were used to determine linearity by two methods.

LOD/LOQ

The limit of detection (LOD) and limit of quantification (LOQ) were calculated by using formula. Calibration curve was repeated for five times and standard deviation (SD) of the intercepts was calculated.

Accuracy

The accuracy of the method was carried out by spiking triplicate at three different concentration levels 50,100 and 150% (5, 10 and 15µg/mL for ROS and 30, 60 and 90 µg/mL for FIM) to placebo. The accuracy of method was evaluated by calculating the percentage recovery.

Precision

Repeatability was performed under 6 replicates at concentration of 10 µg/mL of ROS and 60 µg/Ml of FIM. Intra-day and inter-day variations Specificity of ROS and FIM were performed in triplicate at three different concentration levels 50, 150, 250% (1, 3, and 5 µg/mL) for Etoricoxib and Paracetamol were performed in triplicate at three different concentration levels 50, 150, 250% (5, 15, and 25 µg/mL) for ROS and (30, 90, 150 µg/mL) for FIM. The results were presented in the form of RSD.

Assay preparation

Sample Stock Solution

Weight about sample (equivalent to 60mg of FIM/10mg of ROS) into a 100ml volumetric flask. Add 100ml methanol, 5mg Barium sulphate and put this volumetric on water bath

at 60 °C for 15 minutes then allow to cool at room temperature. Shake for 15 minutes. Make up volume with methanol up to 100ml. Filter this solution with whatman filter paper no-1. (ROS-100mcg/ml, FIM-600mcg/ml)

Working Sample Preparation

Take 1ml from sample stock solution into a 10ml volumetric flask and make up with mobile phase. (ROS-10mcg/ml and FIM-60mcg/ml)

Results and Discussion

Linearity and Range

The linearity study was carried out for both drugs at different concentration levels. The linearity of ROS and FIM was in the range of 5-30µg/ml for ROS and 30-150 µg/ml. % RSD of all results were less than 2%.

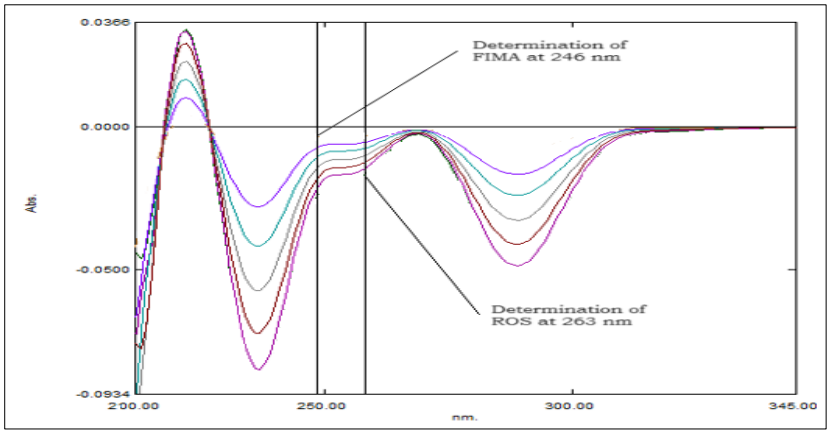

Fig 3: Overlain D^1 spectra of mixture of FIMA (30-150 µg/mL) and ROS (5-25 µg/mL)

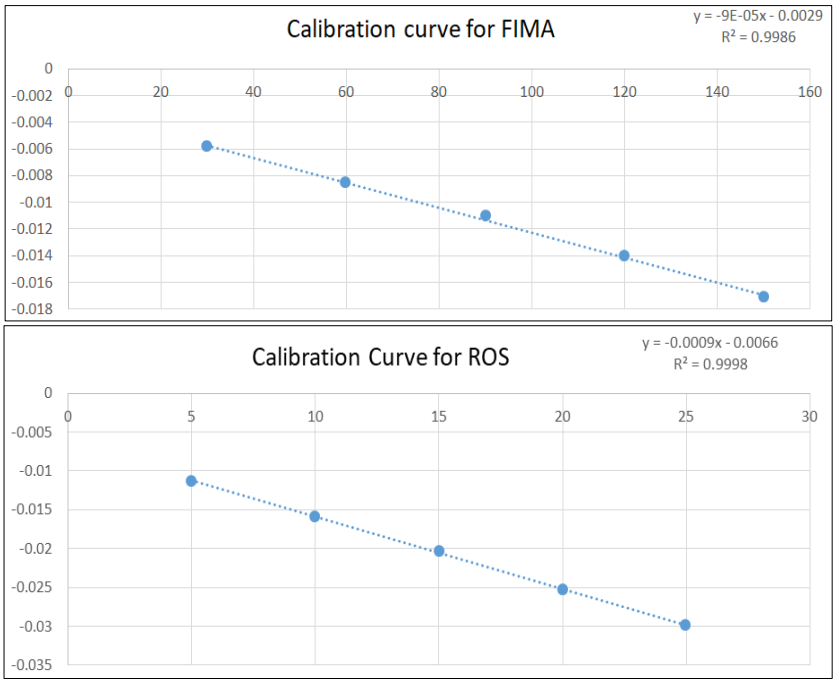

Fig 4: Calibration curve of ROS and FIM in UV

Table 1: Linearity data for ROS and FIM in UPLC

Conc(mcg/ml)		Abs	
FIMA	ROS	FIMA	ROS
30	5	-0.00582	-0.01126
60	10	-0.00858	-0.0159
90	15	-0.01106	-0.02046
120	20	-0.0141	-0.02538
150	25	-0.01708	-0.02988
Correlation coefficient		0.9986	0.9999

Table 2: Result of LOD and LOQ in UV

Parameters	FIMA	ROS
LOD	0.661445 µg/ml	0.491935 µg/ml
LOQ	2.004378 µg/ml	1.490712 µg/ml

Accuracy

Table 3: Accuracy study of UV method

Drugs	Amount of drugs (µg/ml)	% of std added	Total amount added	Amount found (µg/ml)	% Recovery (Mean ± SD)	% RSD
ROS	10 (N=3)	50%	5	5.02	100.40 ±0.60	0.59
		100%	10	9.97	99.67 ± 0.68	0.68
		150%	15	14.90	99.31 ± 0.27	0.27
FIM	60 (N=3)	50%	30	47.98	98.60 ± 0.70	0.70
		100%	60	60.2	99.58 ± 1.31	1.31
		150%	90	72.5	98.71 ± 0.79	0.80

Precision

Table 4: Intraday and interday precision of ROS and FIM in UV

Precision	Conc (µg/ml)	(Mean ± SD) (N=3)	% RSD	Conc (µg/ml)	(Mean ± SD) (N=3)	% RSD
Intraday	5	-0.01136 ± 0.000152	-1.34	30	-0.058± 0.00010	-1.72
	15	-0.02053 ± 0.000153	-0.74	90	-0.01093± 0.000153	-1.39
	25	1774.513± 0.000152	-0.51	150	-0.01713± 0.000208	-1.21
Interday	5	-0.01133±0.000153	-1.37	30	-0.0056± 0.00010	-1.78
	15	-0.02077±0.000151	-0.73	90	-0.0109± 0.00010	-0.91
	25	-0.297±0.00010	-0.33	150	-0.0168± 0.00010	-0.59

Repeatability

Table 5: Repeatability study of UV method

ROS		FIM	
Mean ± SD (N=6)	%RSD	Mean ± SD (N=6)	%RSD
-0.0159± 0.00010	-0.62	-0.00858± 0.00008	-0.97

Table 6: Analysis of physical mixture

Drugs	Amount taken	%Amount of drug found	%RSD
ROS (N=3)	10 µg/ml	99.30%	0.79
FIM (N=3)	60 µg/ml	98.84%	0.85

Table 7: Summary of validation parameters

Parameter	Fimasartan	Rosuvastatin
Linearity		
Regression Equation	y =-9E-05x-0.0029	y =-0.0009x-0.0066
Regression Co-efficient (R^2)	0.9986	0.9999
Slope	0.00074	0.0009
SD	0.00014	0.00013
Range (µg/ml)	30-150 µg/ml	5-30 µg/ml
Precision		
Intraday Precision (N=3)	-1.44	-0.86
Interday Precision (N=3)	-1.09	-0.831
L.O.D (µg/ml)	0.661445 µg/ml	0.491935 µg/ml
L.O.Q (µg/ml)	2.004378 µg/ml	1.490712 µg/ml

Conclusions

Simple UV spectrophotometric methods were developed for the simultaneous determination of Rosuvastatin and Fimasartan in synthetic mixture without any interference from the excipients. To the best of our knowledge, the present study is the first report for the purpose. The present methods succeeded in adopting a simple sample preparation that achieved satisfactory extraction recovery and facilitated its application in coformulated formulation.

The results of our study indicate that the proposed UV spectroscopic methods are simple, rapid, precise and accurate. Statistical analysis proves that, these methods are repeatable and selective for the analysis of ROS and FIM. It can therefore be concluded that use of these methods can save much time and money and they can be with accuracy.

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Conflict of Interest

The authors declare no conflict of interest.

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