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Original Article

Highly sensitive carboxyl group fluorimetric derivatization HPLC analysis for rosuvastatin content in tablets

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ABSTRACT

Background and Aims: The powerful antihyperlipidemic drug rosuvastatin blocks 3-hydroxy-3-methylglutaryl coenzyme A reductase, which is essential for cholesterol formation. Statins are a more recent class of antihyperlipidemic medications. Accurate quantification methods are crucial because of low rosuvastatin levels in tablets. The following the International Conference on Harmonisation (ICH) guidelines, a sensitive and high-performance liquid chromatographic approach was established in this study for the accurate determination of rosuvastatin in tablet formulations using spectrofluorimetric detection.

Methods: The procedure requires one hour at room temperature and dark interaction between the acid group of rosuvastatin and the reagent 9-anthryldiazomethane. A C18 column (250 x 4.6 mm, 4 µm) was used for the gradient elution of an acetonitrile-water solution at a flow rate of 1.0 mL/min to achieve chromatographic separation. The internal reference was lovastatin. The excitation and emission wavelengths used for the detection were 366 and 410 nm, respectively.

Results: Calibration curves for standard solutions were established by plotting the ratio of concentration to peak area over the range 0.01–20.0 ng/mL. The limits of quantification (LOQ) and detection (LOD) were 0.0068 and 0.0023 ng/mL, respectively. The relative standard deviation values for interday and intraday measurements of the standard solutions ranged from 0.24% to 3.76%. The mean recoveries for 0.240. in the tablet formulation were calculated as 98.0-99.9%.

Conclusion: The developed method was used to determine the amount of rosuvastatin in tablets, and the results were compared with a 95% confidence level to those obtained using a literature method. The suggested approach works well for sensitive routine analysis and monitoring of drugs at low concentrations to investigate their bioavailability and bioequivalence.

Keywords: Derivatization, Fluorescence, HPLC, Rosuvastatin, Statin, Tablet

INTRODUCTION

Recently, humans have become more susceptible to hyperlipidaemia because of the rise in animal products and decline in physical activity caused by recent technological breakthroughs. Atherosclerosis and coronary heart disease (CHD) are linked to hyperlipidaemia. The goal of CHD treatment is to lower hyperlipidaemia. Because they block the enzyme 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase, statins are prescribed to people with high blood cholesterol who are at risk of cardiovascular disease. Since 1987, these medications have been the most successful means of treating hyperlipidaemia (Onat, Sansoy, Hergenç, Soydan, & Adalat, 2009). Early-stage CHD and high-risk patients without CHD respond well to statin treatment (Taylor et al., 2013).

The newest statin, rosuvastatin (ROS), decreases low-density lipoprotein cholesterol (LDL-C), total cholesterol, and triglycerides and raises high-density lipoprotein levels. It also has a stronger low-density lipoprotein (LDL)-lowering effect than other statins (Martin, Mitchell, & Schneck, 2002; Carswell , Plosker, & Jarvis, 2002). Figures 1 and 2, respectively, show the chemical structure, UV spectrum, and fourier transform infrared spectroscopy (FT-IR) spectrum of ROS in acetonitrile. ROS is soluble in acetonitrile, water, and methanol and has a pKa value of 3.8.

Currently, several high performance liquid chromatography (HPLC) methods have been developed for measuring ROS in a variety of matrices, either alone or in conjunction with other medications. According to several studies (Lakshmana, & Suneetha, 2010; Sankar, Kumar, & Krishna, 2007; Hemant Kumar, Swathi Sri, Vara Prasada Rao, & Srinivasa Rao, 2015; Moid et al., 2018; Pimpale & Kakde, 2021; Rao &

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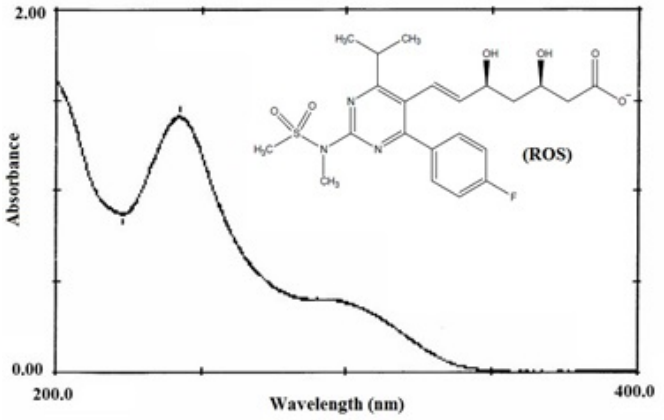

Figure 1. Chemical structure and UV spectrum of 8 µg/mL ROS in acetonitrile

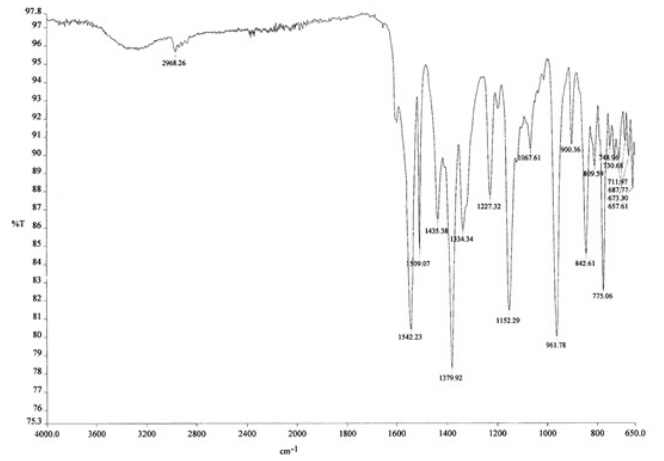

Figure 2. FTIR spectra of ROS

Suneetha, 2010), these techniques were developed for assessing ROS in bulk and pharmaceutical dosage forms. Chromatographic stability-indicating techniques have been successfully applied by Hasumati, Sadhana, Jayant, & Patel, (2009); Krishnaiah et al. (2009), Tushar, Patel, Kulkarni, & Suubbaiah, (2005); Gomes et al. (2009); Anuradha & Plaur (2016); Gholve, Pekamwar,Wadher, & Kalyankar, (2021); Hamdy, Korany, Ebied, & Haggag, (2022) for determining ROS in pure form and pharmaceutical preparations.

HPLC-UV was used to determine ROS in combined dosage forms in the following studies: Janardhanan, Manavalan, & Valliappan, (2016); Kumar, Kumar, Kumar, & Patel, (2017); Mostafa, El-Ashrey, & Mahmoud, (2023); Zuromska-Witek, Stolarczyk, Szlósarczyk, Kielar, & Hubicka, (2023); Albishri, Al-Shehri, Alshitari, & El-Hady, (2024); Alshitari, Al-Shehri, El-Hady, & Albishri, (2021); Choi, Park, & Kim, (2021); Deshpande & Gunge (2018); Hussain et al. (2022). However, the aforementioned approaches do not provide sensitive quantification because of the low concentration of the ROS active component in tablets.

The process of fluorimetric derivatization is often used to increase sensitivity. 9-anthryldiazomethane (ADAM) (Figure 3) was used as the fluorimetric label for derivatization because ROS contains a carboxylic acid group. Even in the presence of water, the carboxyl functional group reacts with ADAM at room temperature in mild circumstances without the need for an activating reagent. Reversed-phase HPLC can be used to identify these acids at picomole levels because of the derivatives generated (Toyo'oka, 1999).

In this work, ROS and ADAM were subjected to a fluorimetric derivatization reaction, and the reaction product was identified by HPLC in reference solutions. The proposed technique was effectively implemented for tablets, and the outcomes were compared with an HPLC-UV technique documented in existing literature.

This work was part of the principal author's doctoral thesis, and part of it was published in a publication. (Caglar, & Toker, 2012).

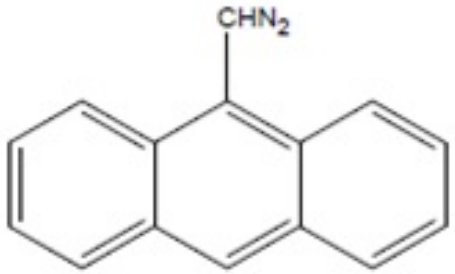

Figure 3. Chemical structure of ADAM

MATERIALS AND METHODS

Chemicals, reagents, and solutions

ROS calcium was obtained from AstraZeneca (London, UK), and lovastatin was obtained from Merck Sharp and Dohme Corp. (Whitehouse Station, NJ). Crestor 20 mg tablets were purchased from a pharmacy. ADAM was sourced from Sigma-Aldrich (Oslo, Norway). Sodium acetate, acetonitrile, ethyl acetate (EA), methyl tertiary butyl ether (MTBE), chloroform, glacial acetic acid, and anhydrous sodium sulphate were acquired from Merck (Darmstadt, Germany). Ultra-pure water was produced using the AquaMAX water purification system (Younglin Instrument (Korea). Lovastatin was used as the internal standard (IS).

A 1.0 mg/mL ROS stock solution was prepared in acetonitrile and diluted with acetonitrile to achieve a concentration of 1 mg/mL. ROS working solutions I and II were prepared at concentrations of 25 ng/mL and 1 ng/mL, respectively, in an acetonitrile–water (1:3) mixture. Solutions of 100 mg/mL ADAM and IS were prepared in acetonitrile and chloroform, respectively.

Derivatization Procedure

We prepared ADAM and IS solutions at concentrations of 100 mg/mL in acetonitrile and chloroform, respectively. Sodium acetate was dissolved in water to achieve a 0.1 M concentration for the acetate buffer solution, with the pH adjusted to 4.0 using glacial acetic acid, as per the US Pharmacopoeia. To prepare ROS base solutions and for derivatization, the same procedure was used as described in (Caglar et al. 2012). All reagent solutions were freshly prepared daily and stored away from light.

To improve the sensitivity and accuracy of ROS analysis, derivatization conditions, including the concentration of ADAM, temperature and time were optimised. Different volumes of 100 mg/mL ADAM reagent solution, ranging from 10 to 200 µL, were used to study the effects of volume and concentration. It was observed that 125 µL of 100 mg/mL ADAM was optimal for the ADAM-ROS derivative (Fig. 4).

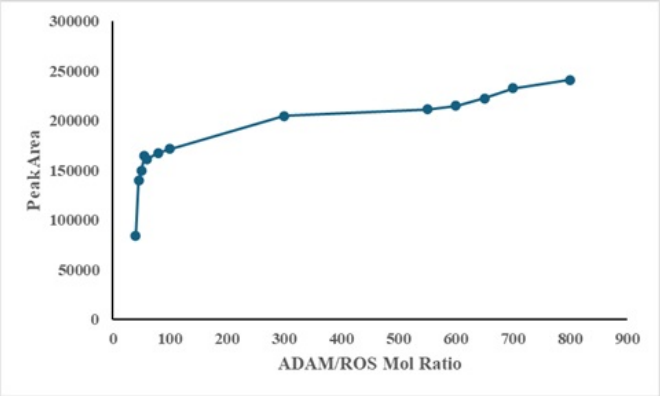

Figure 4. Effect of marker concentration on the formation of the ADAM derivative of ROS

The completeness of derivatization was investigated at different temperatures (room temperature, 30, 40, 50 and 60^0C) and reaction times. ADAM-ROS were completely derivatized at ambient temperature for 1 h. (Fig. 5)

Chromatography

A Shimadzu LC 20A liquid chromatograph equipped with an RF 10 AXL fluorescence detector and LC Solution system software was used during the study (λex=366, λem=410 nm). Separations were performed on a Phenomenex Synergi C18

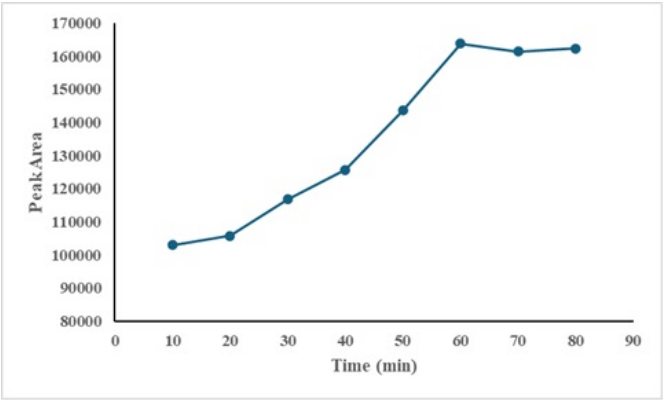

Figure 5. Effect of time on the derivatization reaction

column (4 µm, 250 x 4.6 mm) with a Phenomenex guard column.

The mobile phase, consisting of a mixture of acetonitrile and water, was filtered through a 0.45 µm polytetrafluoroethylene (PTFE) filter (Waters Corporation) and sonicated for 5 min. The analysis was conducted under gradient conditions (Caglar et al. 2012) at a flow rate of 1 mL/min. Lovastatin was used as the internal standard (IS).

Application to pharmaceutical preparations

To determine the average weight of a single Crestor® 20 mg tablet, 10 tablets were weighed separately and ground into a fine powder using a porcelain mortar. A precisely weighed quantity of tablet powder equal to 20 mg of the ROS base was added to a 100 mL volumetric flask. 50 mL of the mobile phase (water: acetonitrile, 40:60) was added to this flask. After 30 min of sonication, the mixture was brought to a volume using the mobile phase and subsequently filtered through blue band filter paper, discarding the first thirty millilitres of the filtrate.

The remaining filtrate was divided into 0.5 mL aliquots and diluted with mobile phase to make 10 mL. After diluting 0.1 mL of this solution with water to make 10 mL, the final volume of the solution was examined using the developed methodology. Six repetitions of this analysis process were conducted. The equation resulting from the previously constructed calibration curve was used to determine the ROS content in the tablets.

Method Validation

For the purpose of validating the developed method, validation criteria like selectivity, linearity, limit of detection (LOD), limit of quantification (LOQ), accuracy, precision, and stability, were assessed in accordance with ICH recommendations (ICH Q2 (R1), 2005).

The assessment of the linearity of ROS was conducted on a sample of six, considering the concentration of ROS in the preparation comprising the injection solution, within the range

of 0.01-20.0 ng/mL. Volumes of 0.4, 40, 200, 400, 600, and 800 µL were extracted from working solution II and subjected to derivatization to investigate linearity. After comparing the peak areas of ROS-ADAM and IS-ADAM, calibration curves were created by plotting the average peak area ratio values against the concentration data.

The formulas LOD or LOQ = SDa/b were used to calculate the values of LOD and LOQ, where a and a are 3, and 10, respectively. SD is the calibration curve intercept, and b is the slope of the calibration curve.

Three distinct concentrations were selected from the calibration curve to assess the absolute recovery. Absolute recoveries were evaluated using the standard addition method. Using the derivatization process, standard solutions of ROS at concentrations of 1.0, 5.0, and 15.0 ng/mL (n=6 each) were prepared, and the developed method was used for analysis.

Assessments of intra- and inter-day precision were part of the precision studies. On the same day or on different days, standard mobile phase solutions were prepared and evaluated at concentrations of 1.0, 5.0, and 15.0 ng/mL (n=6 each). The measured values' relative standard deviations (RSD) percentages were computed.

The ROS-ADAM derivatization solution's stability was assessed for 12, 24, 48, 72, and 96 h at 4°C in a dark environment in addition to room temperature.

RESULTS AND DISCUSSION

Method development

Biologically significant carboxylic acids can be sensitively detected at the picomole level using ADAM, a diazomethyl sensor that is frequently employed as a fluorescent label (Toyo'oka 1999). It was selected for derivatization because it can react with carboxyl groups at room temperature in mild circumstances, even in the presence of water, and it does not require an activating reagent. With reversed-phase HPLC, the products of this reaction can be found at picomole levels. The concentration, temperature, and duration of ADAM were carefully adjusted during derivatization in order to maximise the sensitivity and accuracy of ROS analysis. The ideal conditions for the ADAM-ROS derivative were found to be 125 µL of a 100 mg/mL ADAM reagent solution (Fig. 4).

Various reaction times and temperatures (room temperature, 30°C, 40°C, 50°C, and 60°C) were used to evaluate the completeness of the derivatization reaction. After 1 h at room temperature, the reaction between ROS and ADAM was determined to be complete (Fig. 5).

Figure 5 shows how temperature and reaction time affected the ROS-ADAM intensity. Furthermore, by adjusting the mole ratio of ADAM to ROS, the amount of ADAM reagent needed was determined, and it was found that a 55-fold molar excess of reagent was necessary for the entire reaction.

Selectivity

The system was injected with the mobile phase, the ROS-ADAM standard solution, and derivatization reactions (blank solution) without any other compounds to assess the method's selectivity. This made it possible to investigate interferences that might have come from the reagent, the mobile phase, or contaminants in the reaction environment. Furthermore, as shown in Figure 6, no peaks related to the solvent or reaction environment were observed during the ROS retention period, indicating that the proposed approach can isolate ROS-ADAM from any interference or background noise.

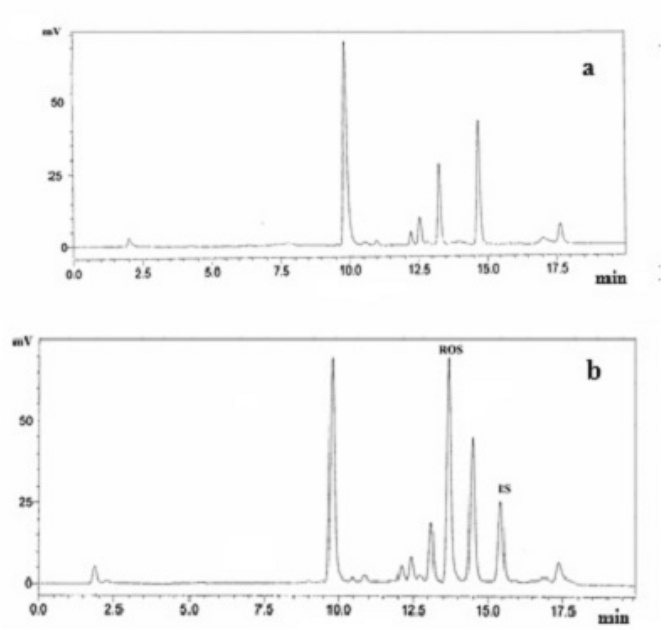

Figure 6. Chromatograms obtained from (a) the blank solution (b) the ROS-ADAM standard solution

Linearity and sensitivity

Over a concentration range of 0.01-20.0 ng/mL, the linearity of the developed approach was evaluated for pharmaceutical ROS formulations. The average regression equation, A = 0.2617±0.0005 C + 0.1566±0.0035 (R2 = 0.9975), was found, where C is the ROS concentration (ng/mL) and A is the peak area ratio. The LOQ and LOD were 0.0023 ng/mL and 0.00068 ng/mL, respectively, based on the study parameters.

Recovery

As shown in Table 1, the absolute ROS recovery values in the tablet formulation were between 98.0% and 99.9 %. The average ROS recovery was 99.2%.

Table 1. Recovery results for the assay of rosuvastatin (n=6)

Concentration (ng mL^{-1})		Recovery (%)	RSD[b] (%)
Added	**Found** (mean ± SD[a])		
1.0	0.98±0.022	98.0	1.909
5.0	4.98±0.023	99.6	0.500
15.0	14.98±0.027	99.9	0.208

[a] Standard deviation; [b] Relative standard deviation

Precision

As previously mentioned, precision evaluations were performed for both intra-day and inter-day repeatability. For intraday repeatability, the relative standard deviation (RSD%) varied from 0.24% to 3.73%, whereas for interday repeatability, it ranged from 0.24% to 3.76%. The precision values derived by the proposed method are displayed in Table 2.

The reliability of the results were demonsrated by the precisionstudy, which also meet the criteria that the RSD% should be less than 3.76%.

Table 2. Intra-day & inter-day precision and accuracy of rosuvastatin (n=6)

Concentration (ng mL^{-1})		RSD[b] (%)	RME[c] (%)
Added	**Found (mean ± SD[a])**		
Intra-day			
1.0	0.99 ± 0.037	3.73	-0.8
5.0	4.98 ± 0.049	0.98	-0.44
15.0	14.98 ± 0.036	0.24	-0.08
Inter-day			
1.0	1.01 ± 0.038	3.76	0.6
5.0	4.99 ± 0.037	0.75	-0.2
15.0	14.98 ± 0.036	0.24	-0.1

[a] Standard deviation; [b] Relative standard deviation; [c] Relative mean error

Stability

Stability study was conducted to assess the derivative by keeping it in the dark at room temperature and at +4°C for 12, 24, 48, 72, and 96 h. It was found that the derivative remained stable for up to 96 h when stored at +4°C and in the dark, as summarised in Table 3.

Table 3. Stability of rosuvastatin obtained using the proposed method

	Peak Area					
	0. hour	**12. hour**	**24. hour**	**48. hour**	**72. hour**	**96. hour**
dark at room temperature	172826	171634	170878	170176	169978	169176
the dark at +4°C	172856	172873	172435	172291	171792	171886

Determination of ROS from the tablet and comparison of the results

The tablets were also examined using the HPLC-UV technique described in the literature to compare the outcomes (Mehta, Patel, Kulkarni, & Suubbaiah, 2005). Table 4 displays the findings from both approaches, as well as the average values (Amean), standard deviation (SD), relative standard deviation (RSD), and 95% confidence level confidence interval [Amean ± (t.s/-n)], which were computed from 6 determinations.

Table 4. Statistical evaluation of the analysis results using the comparison methods

Statistical value	HPLC Metod*	Comparision Method
Mean± SD	19.902±0.048	19.942±0.06
RSD (%)	0.24	0.30
Confidence interval	0.0273	0.0336
Confidence limits	19.875-19.929	19.908-19.976
Student's t-test **	1.387	
F-test**	1.52	

**p = 0.05, t = 2.228, F = 5.05, [a*] Crestor tablet® (20 mg Rosuvastatin)

Student's t-test was used to compare the average results between the developed and reference methods, and Fisher's F-test was used to compare the standard deviation. After checking through Table 4's results, it was discovered that, at a 95% probability level and six trials, the computed t- and F-values were less than the crucial values listed in the corresponding tables. As a result, it was determined that there was no discernible variation in accuracy or precision between the reference technique and the proposed HPLC method.

CONCLUSION

In conclusion, a novel HPLC technique was developed for the sensitive, reliable, and repeatable identification of ROS in plasma and pharmaceutical formulations. By taking advantage of the simple interaction between ROS and ADAM, the approach does not require re-extraction from the reaction medium. The main benefits of this approach are its high recovery rates, good repeatability, and ease of use in terms of both the chromatographic equipment and detector setup. Therefore, it is suitable for routine pharmaceutical analyses and tracking low drug concentrations in bioavailability and bioequivalence research.

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