Analytical Method Validation on Estimation of Rotigotine in Pharmaceutical Formulations

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Abstract

A stability-indicating analytical method was developed for quantifying Rotigotine in a pharmaceutical microsphere formulation using Reversed-Phase High-Performance Liquid Chromatography (RP-HPLC), following the ICH guidelines. The analysis was carried out on a C8 column (150 mm × 4.6 mm; 5 µm particle size) with the column oven maintained at 40 °C. The mobile phase consisted of two components: Mobile Phase A - orthophosphoric acid and triethylamine in purified water (1:1:1000), and Mobile Phase B - acetonitrile, applied in gradient mode. The chromatographic conditions included a flow rate of 1.0 mL/min, a sample temperature of 25 °C, and a diluent comprising water, acetonitrile, and triethylamine (500:500:1). The injection volume was set at 20 µL, with ultraviolet-visible (UV-Vis) detection at a wavelength of 278 nm and a total run time of 15 minutes. All system suitability parameters met the requirements specified by the FDA. The precision of the method was demonstrated through six replicate preparations, yielding assay values ranging from 99.34% to 100.27%. The calibration curve, plotted across 80% to 120% of the target concentration, exhibited a coefficient of determination (R^2) of 0.9998. Recovery studies within the same concentration range showed recoveries between 100.10% and 100.13%. The method showed a limit of detection (LOD) of 0.010 µg/mL and a limit of quantification (LOQ) of 0.035 µg/mL for Rotigotine. To verify that the assay functions as a true stability-indicating method, forced degradation experiments were carried out to evaluate the stability of Rotigotine within the pharmaceutical microsphere formulation.

INTRODUCTION

Rotigotine (ROG) is a non-ergoline dopamine receptor agonist that has garnered significant attention in the field of neurology due to its unique pharmacodynamic profile and therapeutic potential [1], [2]. Unlike ergoline-derived dopamine agonists, ROG exhibits a lower risk of adverse effects such as fibrosis and valvulopathy, making it a safer alternative for long-term treatment of Parkinson's disease (PD) and restless legs syndrome (RLS) [3], [4].

The Rotigotine Transdermal System (RTS), approved by the US FDA in May 2007, represents a significant advancement in the delivery of ROG [5], [6]. The transdermal route offers several advantages over traditional oral administration, including bypassing first-pass metabolism, providing consistent plasma concentrations, and reducing gastrointestinal side effects [7]. The formulation is offered in six dosage levels, with strengths between 1 mg/24 h and 8 mg/24 h, allowing for individualized dosing based on disease severity and patient response. In Parkinson's disease, the advised dose lies between 2–8 mg/24 h, whereas for RLS, a lower range of 1–3 mg/24 h is generally used [8]. This flexibility in dosing underscores the importance of RTS in achieving optimal therapeutic outcomes while minimizing adverse effects.

Chemically, ROG is a structurally (Fig. 1) described as "(6S)-6-{propyl[2-(2-thienyl)ethyl]amino}-5,6,7,8-tetrahydro-1-naphthalenol." It has the molecular formula $C_{19}H_{25}NOS$ and a molecular weight of 315.48 g/mol. Its crystalline form significantly influences its solubility and stability—two key attributes that

directly impact its formulation and overall delivery performance [9]. The physicochemical properties of ROG, including its functional groups, play a pivotal role in its analytical detection and quantification. These attributes are particularly relevant when developing novel drug delivery systems, such as microspheres, which aim to provide controlled and sustained release of the active ingredient [10].

The innovator formulation of ROG, marketed as NEUPRO™, is a transdermal system that comprises a drug matrix layer containing ROG along with excipients including ascorbyl palmitate, povidone, silicone adhesive, sodium metabisulfite, and dl-α-tocopherol [11]. These excipients enhance the formulation's stability, adhesion, and overall efficacy. While NEUPRO™ has proven effective in delivering ROG through the skin, exploring alternative delivery systems, such as microspheres (MS), has introduced new analytical challenges. Microspheres enable the development of extended-release formulations, thereby enhancing patient adherence and therapeutic efficacy [12]. However, the absence of established analytical methods for quantifying ROG in such novel delivery systems represents a significant gap in the current literature [13], [14], [15], [16].

The development of a robust, simple, and selective analytical method for the quantification of ROG in Rotigotine-microspheres (ROG-MS) formulations is therefore of paramount importance. RP-HPLC was chosen for this purpose due to its high resolution, reproducibility, and suitability for analyzing compounds with diverse physicochemical properties [17]. RP-HPLC is a widely used technique in pharmaceutical analysis, offering the ability to separate, identify, and quantify complex mixtures with high precision and accuracy [18], [19], [20]. In compliance with ICH guidelines, the method underwent optimization and validation, ensuring accuracy, reproducibility, and relevance for both research and pharmaceutical development. [21], [22].

This study aims to address the critical need for a reliable analytical method to quantify ROG in ROG-MS formulations. By developing and validating an RP-HPLC method, this research provides a foundation for further studies on the controlled release and therapeutic efficacy of ROG in advanced drug delivery systems. The successful implementation of this method will facilitate the development of innovative formulations that enhance the therapeutic potential of ROG, ultimately contributing to better daily functioning and well-being in patients with Parkinson’s disease and RLS.

MATERIALS AND METHODS

Materials

Rotigotine (ROG) was generously provided by MSN Labs, Hyderabad, India. HPLC-grade solvents were used in this study, obtained from MERCK/RANKEM (India), while all other chemicals and reagents were of analytical grade.

Instrumentation

Chromatographic analysis was conducted using a Waters Alliance 2695 RP-HPLC system equipped with a 2489 photodiode array detector, quaternary pump configuration, and an autosampler.Data acquisition and processing were carried out using the Waters Empower workstation.

Development and Optimization of Chromatographic Conditions

A variety of aqueous and organic phase compositions, including organic solvents and buffer solutions, were utilized to optimize the estimation of ROG and establish a reliable and effective chromatographic method.

Chromatographic conditions

Chromatographic separation was carried out using a Hypersil BDS C8 column (150 mm × 4.6 mm, 5 µm). A gradient elution program (Table 1) was applied, achieving complete analysis within 15 minutes at a flow rate of 1.0 mL/min. The column was maintained at 40 °C, and detection was performed with a UV-Vis detector set to 278 nm. An injection volume of 20 µL was used, and all analyses were conducted at an ambient temperature of approximately 25 °C.

Preparation of Mobile Phase A: A mixture of orthophosphoric acid, triethylamine, and purified water was prepared in a 1:1:1000 (v/v/v) ratio and thoroughly blended.

Preparation of Mobile Phase B: Acetonitrile.

Preparation of Diluent: Purified water, acetonitrile, and triethylamine were mixed thoroughly in a 500:500:1 (v/v/v) ratio.

Preparation of Needle Wash: Purified water and methanol were blended in a 20:80 (v/v) ratio and mixed thoroughly.

The retention time was observed at about 8.2 minutes for ROG (for information only).

RESULTS AND DISCUSSION

An RP-HPLC method, capable of indicating stability, was developed in accordance with ICH guidelines to determine ROG in pharmaceutical formulations.

Development and Optimization of Chromatographic Conditions

Various combinations of aqueous and organic phases, as well as adjustments in flow rate and detection wavelength, were systematically explored to refine the chromatographic conditions for accurate ROG quantification. The optimized chromatographic method employed an aqueous mobile phase (A) containing triethylamine, trifluoroacetic acid, and water in a 1:1:1000 (v/v/v) composition, together with an organic phase (B) comprising methanol and acetonitrile at a 700:300 (v/v) ratio. Separation was achieved using a flow rate of 0.8 mL/min, UV detection at 230 nm, and a column temperature of 30 °C.

Under these conditions, ROG exhibited a distinct peak; however, the peak shape was found to be irregular.

To address this issue and enhance peak symmetry, the mobile phase composition was adjusted. The finalized optimized method utilized an aqueous mobile phase (A) containing triethylamine, orthophosphoric acid, and water in a 1:1:1000 (v/v/v) ratio, paired with an organic phase (B) composed solely of acetonitrile. The detection wavelength was set at 278 nm, the column oven temperature maintained at 40 °C, and the flow rate increased to 1.0 mL/min. These modifications resulted in improved ROG estimation with a well-defined and symmetrical peak. The optimized method met all system suitability parameters by FDA guidelines [22]. A representative chromatogram of the ROG standard solution is presented in Fig. 2.

Analytical Method Validation

The analytical procedure for ROG quantification was validated following the ICH Q2 (R1) guideline, encompassing evaluations of system suitability, system precision, specificity, method precision, ruggedness (intermediate precision), linearity, sensitivity, accuracy, range, robustness, filter compatibility, and forced degradation to confirm its stability-indicating performance [26].

System suitability

System suitability was evaluated by preparing a standard ROG solution and injecting it five times. The results are presented in the Supplemental File (Tables S1 & S2). Theoretical plates for the ROG peak in the standard solution were 3604 (acceptance criterion ≥2000), and the tailing factor was 1.18 (acceptance criterion ≤2.0). The %RSD for the five replicate injections was 0.10%, remaining well below the acceptance threshold of 2.0%. All evaluated system suitability parameters complied with the FDA-recommended criteria [22].

System Precision

System precision was assessed by preparing the standard ROG solution and performing six consecutive injections following the established analytical procedure. The corresponding data are presented in the Supplemental File (Table S3). The %RSD of the ROG peak areas across the six injections was 0.09%, well within the acceptance limit of less than <2.0%.

Specificity

Individual impurity solutions, the ROG sample, placebo, and impurity-spiked ROG samples were prepared and subjected to analysis, with the findings summarized in Table 2. The peak purity of ROG in the spiked sample satisfied the established acceptance criteria, and all process-related impurities were effectively separated from the ROG peak. Representative chromatograms for the blank and spiked samples are presented in Figures 3 and 4, respectively. The absolute differences in % assay obtained during specificity assessment are detailed in the Supplemental File (Table S4).

Method Precision

Method precision was determined by analyzing six independently prepared sample solutions of the ROG formulation at the working concentration.

Ruggedness (Intermediate Precision)

The ruggedness of the method was assessed by analyzing six independently prepared ROG formulation samples at the working concentration, employing variations in analysts, instruments, reagents, laboratories, columns, and analysis days. Comprehensive details on the experimental variations, system suitability metrics, peak responses, and outcomes for both method precision and intermediate precision are presented in the Supplemental File (Tables S5–S8). All % assay values from the six preparations fell within the predefined limits (95–105%), and the %RSD for these measurements was below 2%. When combining the 12 data points from method and intermediate precision, the overall %RSD remained below the acceptance threshold of 3%, confirming the robustness of the analytical procedure.

Linearity

ROG composite solutions at five concentration levels (80%, 90%, 100%, 110%, and 120%) were prepared from the standard stock solution, and each was analyzed in triplicate to evaluate linearity. Calibration plots were generated by correlating the solution concentrations with their respective peak areas (mAU) over the range of 0.8–1.2 µg/mL. The linearity data are presented in Table 3, with the corresponding calibration curve shown in the Supplemental File (Figure S1). The correlation coefficients for ROG were ≥0.999, demonstrating excellent linearity and strong agreement with the regression parameters of the calibration model.

Sensitivity

The sensitivity of the method was assessed by calculating the limit of detection (LOD) and limit of quantification (LOQ) using the standard deviation of the intercept (σ) and the slope (S) of the calibration curve [26]. These values were obtained using the equations:

$$LOD = 3.3 \times \sigma / S$$

$$LOQ = 10 \times \sigma / S$$

Based on these calculations, the LOD and LOQ for ROG were found to be 0.010 µg/mL and 0.035 µg/mL, respectively.

Accuracy or Recovery

ROG composite solutions at 80%, 100%, and 120% concentrations were prepared in triplicate and analyzed to assess method accuracy.Recovery was assessed using a component-recovery strategy, in which the measured (recovered) concentration was compared with the known spiked amount. The outcomes, summarized in Table 4, showed individual recoveries ranging from 97.0% to 103.0%, with

mean values between 98.0% and 102.0%. The %RSD for all concentration levels remained below 2%, demonstrating excellent method accuracy.

Range

Method validation was performed over the 80–120% concentration range of ROG, covering precision, accuracy, and linearity. All system suitability and validation parameters complied with the established acceptance limits outlined in the ICH guidelines [26].

Robustness

Method robustness was assessed by systematically varying the flow rate and column oven temperature. For each condition, standard and sample solutions were analyzed, with only a single parameter altered at a time while all other variables were held constant. Retention times and assay results are summarized in Table 5, while details of the varied parameters, system suitability metrics, and observed peak areas during robustness testing are provided in the Supplementary Information (Tables S9–S11). The assay results for ROG remained within the acceptable range of 95–105%.

Bench Top Solution: Stability of Standard Solution and Sample Solutions

The stability of standard and sample solutions containing ROG was evaluated under room temperature conditions. Analyses were performed at the initial time point and after 48 hours to monitor any potential changes in the solutions. Both the standard and sample solutions were found to be stable over the 48-hour period, with no significant degradation observed. The variation in % assay between the initial and 48-hour evaluations remained within ±2.0%, confirming the absence of significant degradation or analytical drift. Furthermore, the similarity factor for the standard solution consistently ranged from 0.98 to 1.02, reflecting high reproducibility of the analytical response. Complete datasets for the solution stability assessment are provided in the Supplementary Information (Table S12).

Bench Top Stability of Mobile Phase

The mobile phase was Stored at room temperature, and its stability was evaluated by examining the standard solution both at the start of the study and again after 48 hours. No haziness or particulate matter was observed during this period, indicating that the mobile phase remained physically stable for up to two days. A summary of the results is provided in the Supplementary Information (Table S13).

Filter Validation

The method was validated for filter compatibility using two types of 0.45 µm filters: Nylon and Polyvinylidene fluoride (PVDF). A homogeneous sample solution of ROG was prepared, and separate portions of this solution were either centrifuged or passed through each filter type before being injected into the HPLC system. Comparative analysis showed that the difference between the filtered samples did not exceed 2%, and all assay values remained within the specified range of 95–105%, demonstrating consistent quantification. No significant interference or variation was observed between the Nylon and

PVDF filters, indicating that both are suitable for sample preparation. Comprehensive details of the filter specifications and corresponding assay results are presented in the Supplementary Information (Tables S14 and S15).

Forced Degradation Study

The stability-indicating nature of the HPLC assay for ROG in the microsphere formulation was assessed by subjecting the samples to multiple stress conditions, including acidic and alkaline hydrolysis, oxidative degradation with hydrogen peroxide, aqueous degradation, elevated temperature, high humidity, fluorescent light, and UV exposure. All stressed samples were subsequently analyzed using the HPLC system, and the outcomes are presented in Table 6. Across all stress conditions, ROG remained stable, with the assay demonstrating consistent quantification. The ROG peak was found to be pure and spectrally homogeneous, confirming that no degradation products co-eluted with the main peak. These findings establish that the method is reliable, specific, and fully capable of indicating stability and detecting potential degradants in the formulation.

CONCLUSION

The results of this study demonstrate that the gradient-elution RP-HPLC method is highly specific, accurate, precise, linear, and robust for reliably quantifying ROG in pharmaceutical formulations. The method exhibited robust performance, maintaining consistent results despite deliberate variations in column oven temperature and flow rate. The method showed both precision and accuracy at the defined limits of detection and quantification, demonstrating reliable performance even at the LOQ. The stability evaluation indicated that the standard and sample solutions retained their stability for as long as 48 hours when kept at room temperature. Similarly, mobile phase stability was maintained for the same duration. Filter validation confirmed the suitability of 0.45 µm Nylon and Polyvinylidene fluoride filters for standard and sample solutions. Forced degradation experiments performed on the ROG formulation verified that the method effectively functions as a stability-indicating procedure. The method validation was carried out following the recommendations outlined in the ICH guidelines, yielding results that support its reliability for ROG measurement via RP-HPLC. This optimized and newly established method is being reported for the first time. With a short run time of 15 minutes, the method is well-suited for routine analysis of ROG across different pharmaceutical formulations and for stability testing. Furthermore, this method holds potential for application in additional studies, including assay development, stability assessments, in vitro release testing, and in vitro permeation studies for future quantitative evaluations.

Declarations

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COMPETING INTERESTS

The authors have no relevant financial or non-financial interests to disclose.

CONFLICT OF INTEREST SECTION

The authors declare that no potential conflicts of interest for this article's research, authorship, and/or publication.

AUTHOR CONTRIBUTIONS

M HIMABINDU (MH)1: The acquisition, analysis, interpretation of data for the work and drafting of the work. **Dr REMYA P N (RPN)1**: The conception, design of the work and final approval of the version to be published. **PURNIMA ASHOK (PA)2:** Provided technical guidance and helped with manuscript correction.

ETHICAL APPROVAL

This article does not contain any studies with human participants or animals performed by any of the authors.

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Tables

Table 1: Gradient Elution Program

Time (Minutes)	Mobile Phase A	Mobile Phase B
0.00	70	30
2.00	70	30
10.00	35	65
12.00	35	65
13.50	70	30
15.00	70	30

Table 2: Specificity Results

Compound Name	Retention Time (Minutes)	Purity Angle	Purity Threshold	Peak Purity
Rotigotine	8.211	0.142	0.275	Pass
Desthienylethyl rotigotine	3.534	Not Applicable		
Rotigotine related compound K	5.184			
Rotigotine related compound C	6.361			
Blank	No interfering peaks were detected at the retention time of Rotigotine.			
Placebo Solution				

Table 3: Linearity data of Rotigotine

Linearity Level	Linearity of Rotigotine	
	Concentration (µ/mL)	Average Area (mAU)
80%	0.803	1725650
90%	0.903	1938754
100%	1.003	2140539
110%	1.104	2359212
120%	1.204	2574457
Correlation coefficient	0.9999	
Coefficient of determination	0.9998	
Intercept	29694	
Slope	2111273	
Regression equation (y = mx + c)	y = 2111273 x + 29694	

Table 4: Accuracy or Recovery data of Rotigotine

Spike Level	Amount added in µg/mL	Amount found in µg/mL	% Recovery	Mean	STDEV	%RSD
80% Level	0.803	0.801	99.837	100.10	0.23	0.23
	0.805	0.807	100.213			
	0.804	0.806	100.251			
100% Level	1.003	1.004	100.129	100.11	0.18	0.18
	1.005	1.004	99.923			
	1.006	1.009	100.291			
120% Level	1.204	1.207	100.237	100.13	0.17	0.17
	1.208	1.207	99.933			
	1.207	1.210	100.213			

Table 5: Robustness data for Rotigotine

S. No.	Condition	Retention Time (Minutes)	Assay (%w/w)
1	Actual	8.21	99.78
2	Low Column Temp.	8.46	99.92
3	High Column Temp.	8.11	100.10
4	Low Flow Rate	8.56	100.13
5	High Flow Rate	8.00	99.64

Table 6: Rotigotine Parameters observed during Forced degradation Study

S. No.	Condition	Assay (% w/w)	Purity Angle	Purity Threshold	Peak Purity
1	Control Sample	100.53	0.142	0.275	Pass
2	Acid Sample (1N HCl, 24 Hr at 60 °C)	100.35	0.156	0.303	Pass
3	Base Sample (1N NaOH, 24 Hr at 60 °C)	100.65	0.155	0.308	Pass
4	Water Sample (24 Hr at 60 °C)	99.50	0.153	0.293	Pass
5	Peroxide Sample (1% H_2O_2, 15 minutes at 60 °C)	99.49	0.156	0.291	Pass
6	Thermal Degradation Sample (60 °C for 48 hours)	100.55	0.152	0.313	Pass
7	White Fluorescent Exposure Sample (1.2 Million Lux Hours)	98.50	0.157	0.297	Pass
8	UV light Exposure Sample (200-Watt hours / square meter)	100.51	0.150	0.289	Pass
9	90% RH Humidity Exposure Sample	98.34	0.160	0.299	Pass

Figures

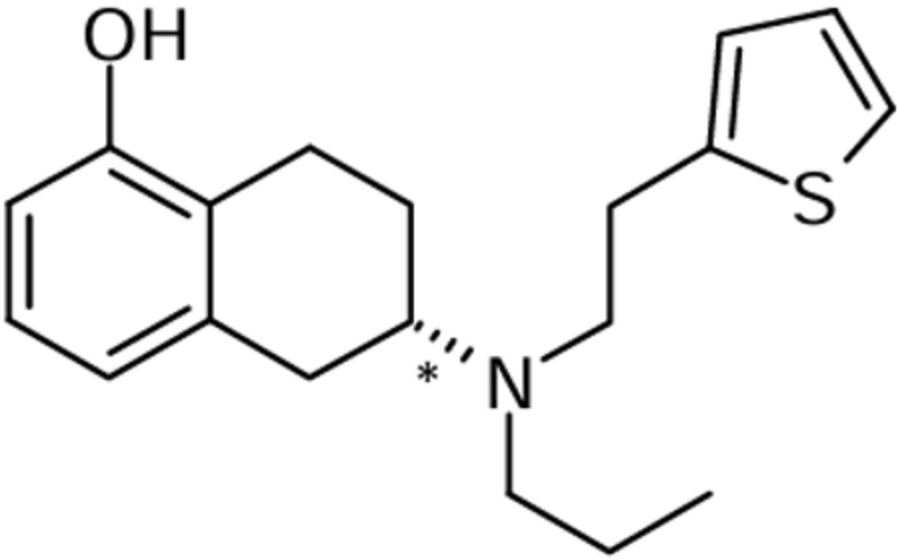

Figure 1

Structure of Rotigotine

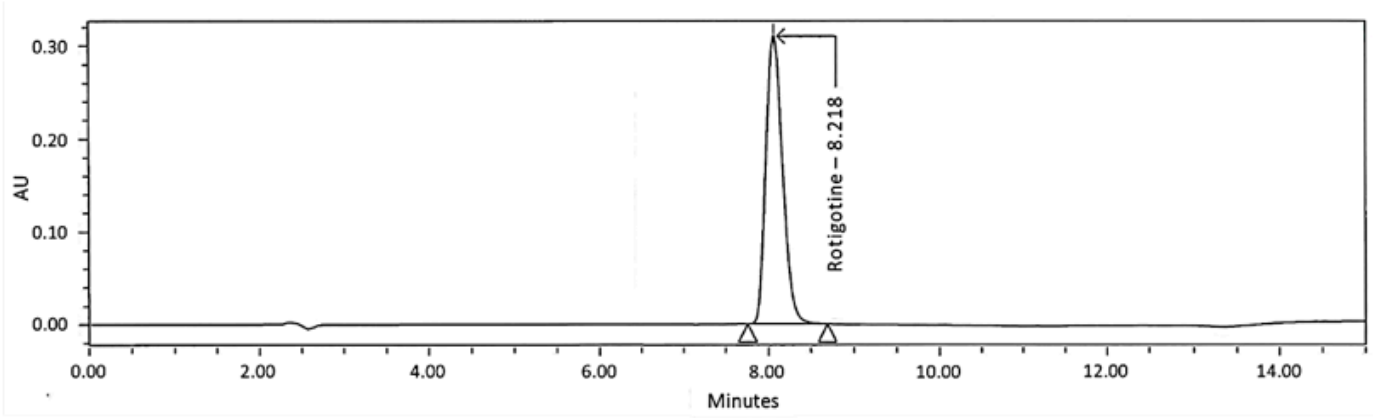

Figure 2

Typical Chromatogram of ROG Standard Solution

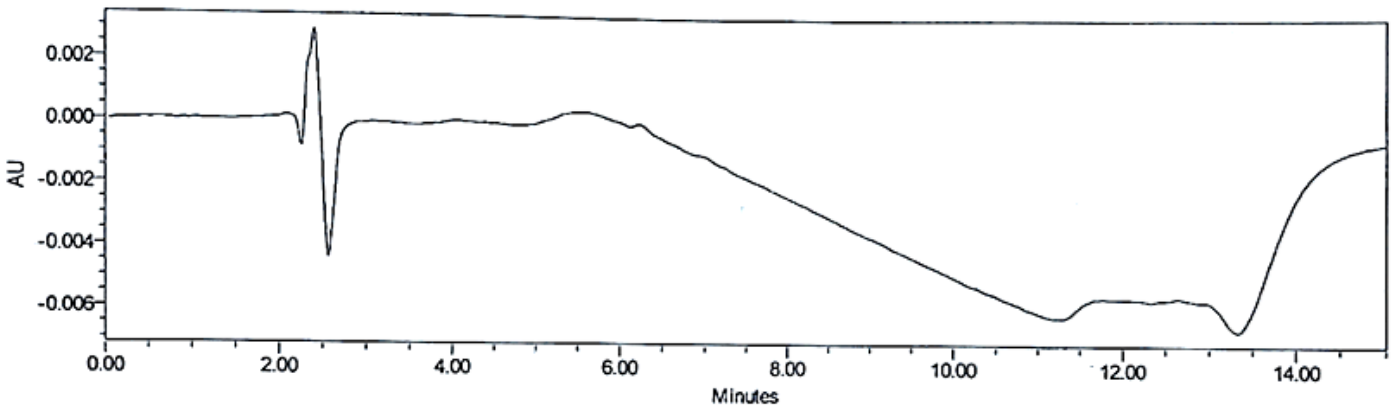

Figure 3

Typical Chromatogram of Blank sample

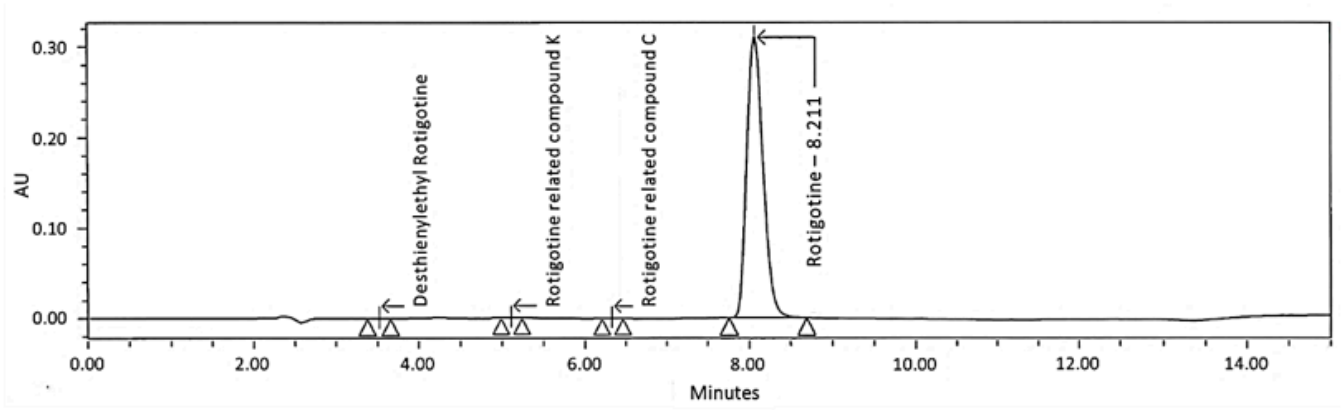

Figure 4

Typical Chromatogram of Spiked sample

Supplementary Files

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