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Research Article

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Development and Validation of a Rapid and Sensitive Ultrahigh-Performance Liquid Chromatography with Diode Array Detection Method for Quantification of Sertraline in Pharmaceutical Formulations

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ABSTRACT

Objective: This study aimed to develop and validate a new, sensitive, fast, and simple ultrahigh-performance liquid chromatography (UHPLC) method for the quantification of sertraline in pharmaceutical preparations and then apply it to commercial pharmaceutical preparations.

Methods: Ultrahigh-performance liquid chromatography with diode array detection was used in the study. In the method, methanol and deionized water containing 0.05% TFA (70 : 30, v/v) were used as the mobile phase, and the C18 column was used as the stationary phase. The flow rate was 1.0 mL/min, the injection volume was 20 µL, and the column temperature was 40°C. The detector was set at 254 nm.

Results: The retention time of sertraline was 2.1 minutes, and the analysis time of the method was 4 minutes. The equation of the calibration curve was determined as $y = 0.1096x - 0.0156$ (R 0.9997). While the limit of detection and limit of quantitation values were 0.1 and 0.3 µg/mL, respectively, the method showed linearity between concentrations of 0.3 and 100 µg/mL. The analytical recovery of the method from the pharmaceutical preparation was within accepted limits (98%-102%). In addition, the relative error percentage and relative standard deviation values, which express the accuracy and precision parameters, respectively, were found to be less than 8%.

Conclusion: In the study, a UHPLC method with high sensitivity and a wide working range was developed for the quantification of sertraline in a short analysis time. As a result, the applicability of the developed method to pharmaceutical preparations has also been proven.

Keywords: Pharmaceutical dosage forms, sertraline, UHPLC-DAD, validation

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INTRODUCTION

Depression is a chronic or recurrent emotional disorder that negatively affects individual behavior. Major depression is a prevalent and debilitating mental illness that affects a significant number of individuals throughout their lifetime, with a prevalence rate of 15%-20%.[1] Antidepressants are the first line of treatment for major depressive disorder, which presents with psychotic and melancholic symptoms. Sertraline (SRT), an antidepressant drug, is a member of the selective serotonin reuptake inhibitors. The chemical name of SRT is (1S-cis)-4-(3,4-dichlorophenyl)-1,2,3,4-tetrahydro-N-methyl-1-naphthal enamine (Figure 1).[2] Sertraline is a potent and selective inhibitor of neuronal serotonin reuptake. It also has very weak effects on neuronal reuptake of norepinephrine and dopamine. For this reason, it is more preferred than tricyclic antidepressants.[3]

In determining the analytical method to be developed for drug analysis, parameters such as the facilities of the laboratory, the chemical properties of the active substance to be analyzed, and the matrix containing the drug should be taken into consideration. A thorough literature review provides an important guide in determining the analytical method to be used in drug analysis. Many studies have been reported in the literature for the determination of SRT in different matrices with different analytical methods. In these studies, spectroscopic,[4-7] high-performance liquid chromatography (HPLC) with

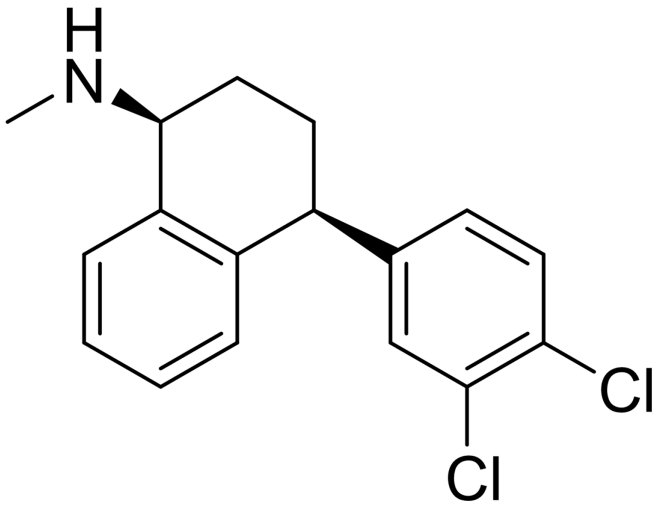

Figure 1. Molecular structure of sertraline.

fluorescence detection,[8] HPLC with ultraviolet detection,[6,7,9-11] gas chromatography (GC),[12-17] capillary electrophoresis-mass spectrometry,[18-20] and liquid chromatography–tandem mass spectrometry (LC-MS/MS)[14,21-23] techniques were used. The high cost of mass spectrometry detectors and the required derivatization step for GC, along with the low sensitivity in spectroscopy, lead to the preference for HPLC in drug quality control analysis.

In this study, a new ultrahigh-performance liquid chromatography with diode array detection (UHPLC-DAD) method was developed as an alternative to the literature that can be used for quality control and stability studies of commercial preparations containing SRT. To ensure the accuracy and reliability of the developed method, various parameters such as specificity, the limit of detection (LOD), the limit of quantitation (LOQ), linearity, precision, accuracy, and robustness were validated. Additionally, forced degradation studies were conducted on the drug product solution to demonstrate method stability and compliance with International Conference on Harmonization (ICH) guidelines.

METHODS

Reagents

Sertraline (99.7% purity, Merck, CAS number: 79559-97-0), a reference standard, was purchased from Sanovel (Istanbul, Turkey). Trifluoroacetic acid (TFA, >99.0% purity), formic acid (FA, >99.0% purity), HPLC-grade acetonitrile, and HPLC-grade methanol were obtained from Sigma-Aldrich (St. Louis, Mo, USA). Ultrapure water was generated by a Milli-Q Plus purification system from Millipore, Waters (Millipore, Bedford, Mass, USA). Three commercial tablets (Selectra® 50 mg tablet (Sanovel), Lustral® 50 mg tablet (Pfizer), and Misol® 50 mg tablet (Nobel)) containing the active ingredient SRT were obtained from the Turkish pharmaceutical market.

Instruments and Chromatographic Conditions

For the analysis of SRT in pharmaceutical formulations, a UHPLC system manufactured by Thermo Scientific® Dionex Ultimate 3000 was employed. The system consisted of a degasser (SR-3000 Solvent Rack), a pump (LPG-3400SD), an autosampler (WPS-3000SL), a column oven (TCC-3000SD), and a diode array detector (DAD 3000). Chromelon software (Thermo Scientific®) was utilized for data acquisition and processing. For chromatographic separation, the Thermo Scientific® column (3 µm 120 Å, LC, 150 × 4.6 mm, C18) was used. The mobile phase consisted of methanol and deionized water containing 0.05% TFA (70:30, v:v). The column temperature was maintained at 40°C during analysis. A 20 µL sample was injected into the system, and the flow rate of the mobile phase was maintained at 1 mL/min. The DAD detector was set at a wavelength of 254 nm.

Preparation Stock, Standard, and Quality Control Solutions

Fifty milligrams of SRT active ingredient was weighed on a sensitive balance and dissolved in a 50 mL volumetric flask with some methanol. After dissolution, the solution was made up to 50 mL with methanol. By diluting this stock solution with methanol, standard working solutions were prepared to determine the calibration curve. Working solutions with concentrations of 0.5, 1, 5, 10, 25, 50, 75, and 100 µg/mL and quality control solutions with concentrations of 4, 40, and 80 µg/mL were prepared.

Preparation of Tablet Solutions

Ten tablets each of Lustral®, Selectra®, and Misol® 50 mg tablet pharmaceutical preparations containing SRT were taken. Each tablet was weighed individually. Thus, the weight of an average tablet was calculated. Ten tablets of each preparation were crushed in a mortar, and the amount of powder corresponding to an average tablet was transferred to a 50 mL volumetric flask. Some methanol was added to 3 volumetric flasks and vortexed. The solution was left to allow the excipients to precipitate. Methanol containing SRT was filtered, transferred to a different 50 mL volumetric flask, and made up to 50 mL with methanol. Thus, stock solutions of 3 pharmaceutical preparations with concentrations of 1 mg/mL were prepared. Two samples, each at 30 and 60 µg/mL concentrations, were prepared from these stock solutions and analyzed by the method.

Optimization of Mobile Phase, Column Temperature, and Detector Wavelengths

Many different experiments were carried out by making changes in the method parameters to determine the chromatographic method conditions. In mobile phase selection, different combinations and compositions of methanol, acetonitrile, water, and an aqueous solution containing 1% FA or 0.05% TFA were tried (Figure 2).

After mobile phase selection, experiments were carried out on different column temperatures (ambient temperature, 25°C, 30°C, and 40°C) to obtain the best peak resolution and retention time. In order to perform the analyses with high sensitivity, they were performed at different wavelengths (254 nm and 290 nm) to determine the wavelength with the highest absorbance (Figure 3).

Method Validation

The method was validated by testing its specificity, linearity, recovery values, LOD, LOQ, and within-day and between-day precision and accuracy. The validation was conducted according to the guidelines set by the ICH for validating analytical procedures.[24]

RESULTS

Specificity (Selectivity)

The blank sample containing only the mobile phase was analyzed. Thus, it was checked whether there was any interference from the mobile phase during the retention time of SRT. Subsequently, standard working solutions containing SRT were injected into the UHPLC system, and chromatograms were obtained. In the

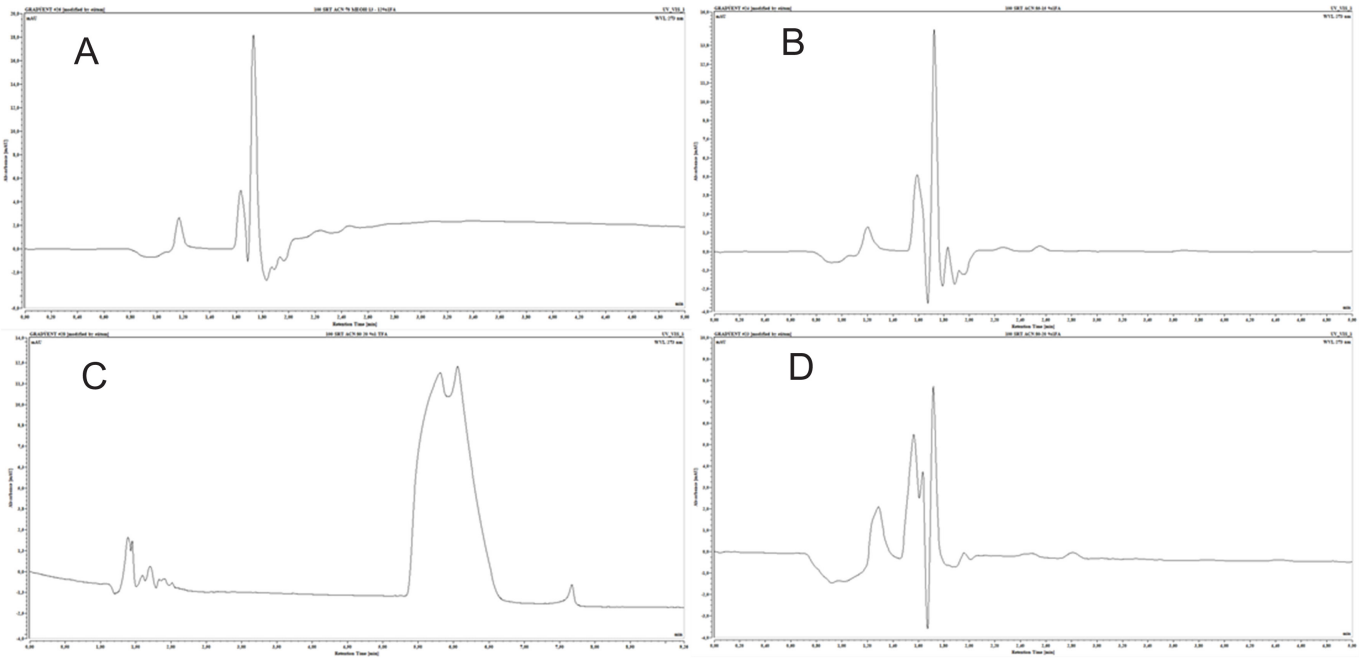

Figure 2. Chromatograms of 100 µg/mL sertraline in different mobile phase experiments. A. Methanol–acetonitrile–1% FA (75:12:13, v:v:v). B. Acetonitrile–1% FA (85:15, v:v). C. Acetonitrile–1% TFA (80:20, v:v). D. Acetonitrile–1% FA (80:20, v:v). FA, formic acid; TFA, trifluoroacetic acid.

chromatogram, the retention time of SRT was determined to be 2.1 minutes (Figure 4).

Linearity and Working Range

The area of the peak obtained from the chromatograms of the standard working solutions for each concentration was plotted against the concentration. The regression analysis of the calibration curve was performed to obtain the equation of the standard curve and the correlation coefficient. The correlation coefficient of the calibration curve formed by 0.3, 0.5, 1, 10, 25, 50, 75, and 100 µg/mL concentrations was found to be 0.9997, and the calibration curve equation was found to be $y = -0.1096x - 0.0156$. The working range was selected as the concentration range where acceptable accuracy, precision, and linearity were achieved. Thus, it was determined that our method showed linearity between 0.3 and 100 µg/mL concentrations (Figure 4).

Accuracy and Precision

Quality control solutions prepared at low, medium, and high concentrations (20, 40, and 80 µg/mL) within the working range were analyzed 6 times with an interval of 3 days. Average concentrations and standard deviation values were determined. Accuracy was expressed as relative error (RE% = (found − added)/added × 100), and precision was expressed as relative standard deviation (RSD% = SD/mean × 100). Relative error percentage and RSD% of the intraday and interday concentration values were found to be less than 8%. Thus, it was determined that the UHPLC method we developed had high accuracy and precision (Table 1).

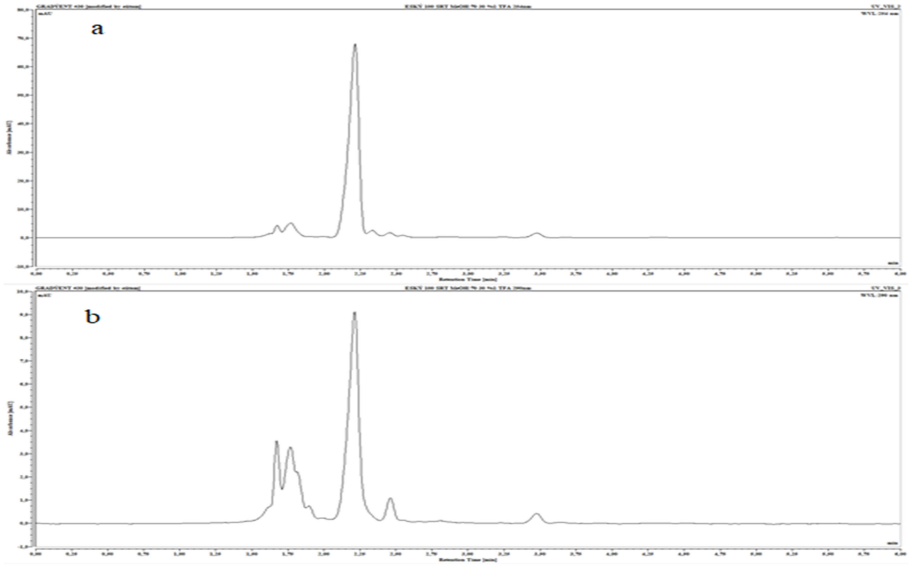

Figure 3. Chromatograms of 100 µg/mL sertraline in different wavelengths. a. 254 nm. b. 290 nm.

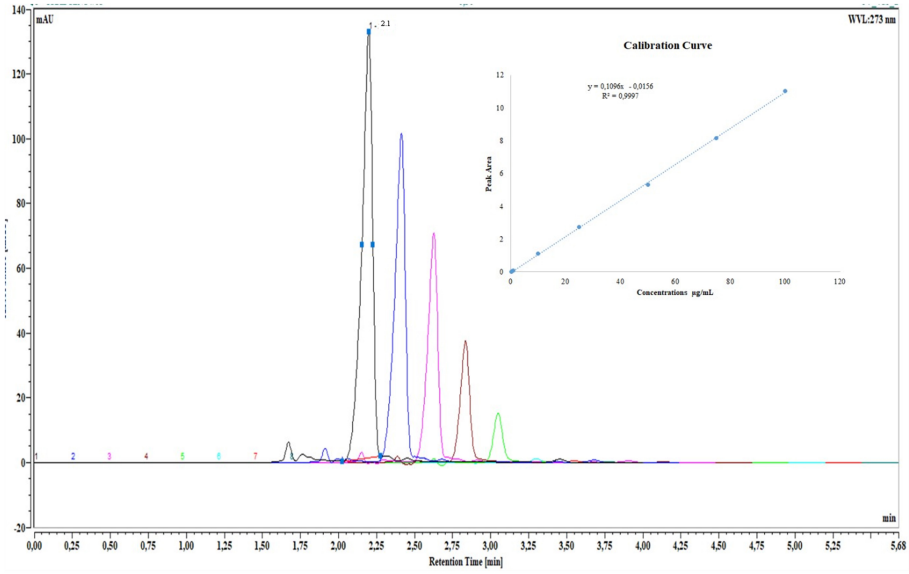

Figure 4. Chromatograms of standard working solutions containing sertraline (0.3-100 µg/mL).

Limit of Detection and Limit of Quantitation

Standard SRT solutions were prepared and analyzed at concentrations lower than the smallest concentration of the working range. By examining the chromatograms, the concentration corresponding to a signal/noise ratio of 3 was determined as 0.10 µg/mL, while the concentration corresponding to a signal/noise ratio of 10 was determined as 0.300 µg/mL (Figure 5).

Analytical Recovery

To conduct analytical recovery studies on a pharmaceutical preparation, the standard addition method was used. First, tablet solutions were prepared as per the instructions given in the "Preparation of Tablet Solutions" section. Chromatograms were obtained for the tablet solutions at a concentration of 5 µg/mL, and the peak areas were determined. Next, standard working solutions at 3 different concentrations (10, 40, and 85 µg/mL) were added to these tablet solutions separately. After obtaining the chromatograms and determining the peak areas, the analytical recovery values were calculated. To obtain these values, the concentrations of the added standard solutions (10, 40, and 85 µg/mL) were subtracted from the total solution concentration (tablet solution + standard solution) and then related to the concentration of the tablet solution (5 µg/mL). Table 2 shows that the average analytical recovery value was 100.2%.

Stability

A stability study of the stock and working solutions of SRT was carried out. After keeping the solutions containing SRT at 30, 60, and 90 µg/mL concentrations at the ambient temperature of 4 and −20°C for 24 and 48 hours, their chromatograms were taken using the HPLC method. By comparing the peak areas with standard solutions with the same concentrations, the results are given as % recovery in Table 3.

Application of the Ultrahigh-Performance Liquid Chromatography with Diode Array Detection Method to Pharmaceutical Preparations

To prove that the developed and validated UHPLC method was applicable to real samples, quantification was performed in 3 different pharmaceutical preparations containing SRT. For this, 3 tablet solutions at 1 mg/mL concentration were diluted, and 2 samples at 30 and 60 µg/mL concentrations for each tablet were analyzed by UHPLC methods and their chromatograms were taken (Figure 6).

DISCUSSION

Chromatography is a technique used in many different fields to separate and quantify chemical components in mixtures. High-performance liquid chromatography, a type of chromatography, stands out with its high accuracy, precision, repeatability, selectivity, sensitivity, recovery, ability to analyze very small sample volumes, rapid determination of results, and low cost compared to alternative techniques. These distinctive features make the HPLC method indispensable in the pharmaceutical industry, especially for the quantitative evaluation of pharmaceutical formulations and the examination of active drug ingredients in different matrices.

In the HPLC technique, the interaction of the components with the stationary and mobile phases, depending on their polarity, determines the way and time they arrive at the detector. Therefore, chromatographic conditions need to be optimized to both separate the components in a short time and obtain peaks with high resolution and short retention times. In this study, during the optimization phase of the UHPLC method developed for the determination of SRT, parameters such as mobile phase, stationary phase, flow rate, temperature, wavelength, and injection

Table 1. Accuracy and Precision Results of the Proposed Method

	Intra-day			Interday		
Added (µg/mL)	Found ± SD (µg/mL)	Accuracy (RE %)	Precision (RSD %)	Found ± SD (µg/mL)	Accuracy (RE%)	Precision (RSD %)
20	20.58 ± 1.12	0.37	1.34	19.88 ± 1.47	−0.74	2.43
40	39.73 ± 0.14	−0.16	2.04	41.37 ± 2.73	2.03	3.15
80	79.63 ± 3.12	−0.39	1.76	80.73 ± 1.36	0.36	1.26

RE%, relative error; RSD%, relative standard deviation; SD, standard deviation of 6 replicate determinations.

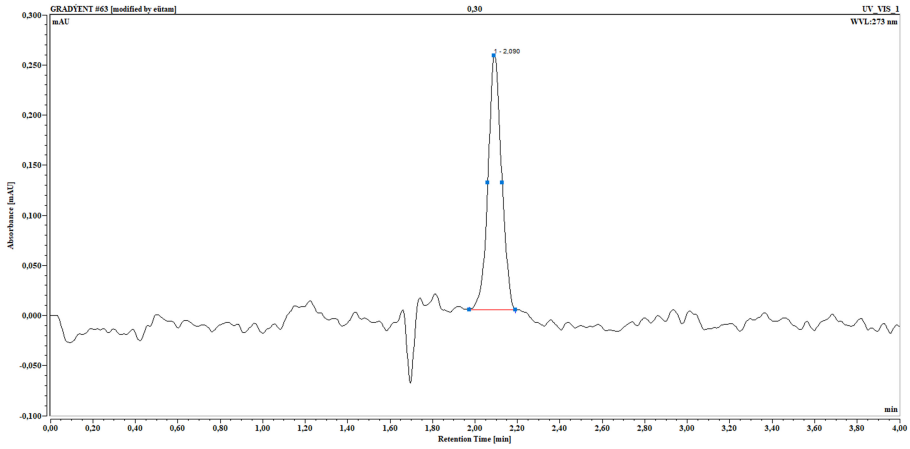

Figure 5. Chromatogram of the sample (0.300 µg/mL) of the limit of quantitation value of the ultrahigh-performance liquid chromatography with diode array detection method.

volume were examined with different modifications by looking at the literature. A reversed-phase C18 column (3 µm, 150 × 4.6 mm) was operated at temperatures of 25, 30, 35, and 40°C as the stationary phase. Flow rates of 0.8-1.2 mL/min and injection volumes of 5-40 µL were tried. Different wavelengths between 240 and 290 nm were tried with the DAD. In mobile phase selection, acetonitrile and methanol solvents were introduced into the system in binary and triple combinations with water, the aqueous solution containing 0.05% TFA, and the aqueous solution containing 1% formic acid. In all these experiments, standard solutions were analyzed one by one, and the results were evaluated. Thus, a new UHPLC method was developed for the quantification of SRT as an alternative to the methods reported in the literature. The developed method was validated by subjecting it to validity tests. The stability of SRT at room temperature, 4°C, and −20°C, at 24- and 48-hour standing conditions showed that more than 95% of SRT remained intact under all conditions compared to standard solutions.

In the study, the retention time of SRT was 2.1, and the analysis time was 4 minutes. Peak areas determined from chromatograms of standard SRT were plotted against concentration. A calibration curve showing linearity over a wide range was derived without the need for derivatization steps applied in spectrophotometric methods reported in the literature. In the

Table 2. Analytical Recovery Values from Tablets

Tablet	Tablet Solutions (µg/mL)	Added Standard Solutions (µg/mL)	Found ± SD (µg/mL)	Analytical Recovery %	RSD%
Lustral® 5 µg/mL	5	10	9.92 ± 0.62	99.9	1.37
		40	40.13 ± 0.16	100.3	2.37
		85	85.92 ± 0.21	100.6	3.61
Selectra® 5 µg/mL	5	10	10.04 ± 0.97	100.1	1.43
		40	41.50 ± 0.53	101.9	2.72
		85	84.10 ± 3.42	98.7	3.47
Misol® 5 µg/mL	5	10	9.81 ± 1.02	99.2	1.04
		40	39.15 ± 2.78	98.9	1.56
		85	86.72 ± 3.47	102.1	2.81

RSD%, relative standard deviation; SD, standard deviation.

Table 3. Stability Studies

Concentrations (µg/mL)	Ambient Temperature 24 hours	Ambient Temperature 48 hours	4°C 24 hours	4°C 48 hours	−20°C 24 hours	−20°C 48 hours
30	98.1 ± 0.14	97.8 ± 3.35	99.8 ± 3.62	98.7 ± 1.59	98.7 ± 0.49	101.3 ± 1.47
60	99.3 ± 0.72	101.3 ± 2.23	99.3 ± 1.57	96.6 ± 2.43	98.3 ± 2.91	99.5 ± 0.93
90	100.2 ± 2.06	99.7 ± 2.68	99.5 ± 2.49	99.2 ± 1.90	99.4 ± 3.20	103.4 ± 0.76

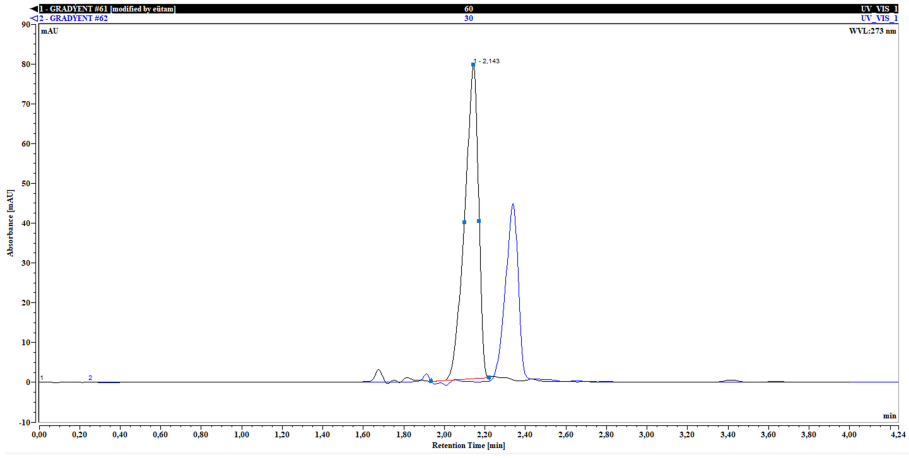

Figure 6. Chromatogram of samples with 30 and 60 µg/mL concentrations prepared from the stock solution of the Lustral® commercial preparation.

regression analysis, the correlation coefficient of the calibration curve was found to be 0.9997, and the calibration curve equation was $y = 0.1096x - 0.0156$. It was determined that the method showed linearity between 0.3 and 100 µg/mL. Using the signal/noise (S/N) ratio, the lowest concentration at which SRT could be detected (LoD) was 0.1 µg/mL (S/N = 3). The concentration at which SRT could be measured with appropriate accuracy and sensitivity (LoQ) was also determined to be 0.3 µg/mL (S/N = 10). In the intraday and interday analyses of quality control solutions prepared at 20, 40, and 80 µg/mL concentrations, RE% and RSD% were found to be lower than 8%. These values show that the UHPLC method has high accuracy and precision. The results of the analytical recovery from the pharmaceutical preparation were within the acceptance limits (85%-120% and RSD% < 8%).

When compared to other spectroscopic methods, the LOQ value of 0.3 µg/mL demonstrates higher sensitivity for the UHPLC method.[4,5] Since the method shows linearity at concentrations of 0.3-100 µg/mL, it offers a wider working range than the reported chromatographic and spectroscopic methods.[6,7,25] Additionally, the following mobile phases were used in previous HPLC studies: methanol: phosphate buffer (pH 4.5) (20 : 80 v/v),[6] acetonitrile and phosphate buffer,[9] acetonitrile–170 mM phosphate buffer, pH 3.0 (adjusted with 85% phosphoric acid) 68 : 32 (v/v),[10] methanol–acetate buffer (pH 2.8, 80 : 20, v/v),[7] and 0.1 M phosphate buffer and acetonitrile.[11] On the other hand, in this research, the use of an aqueous solution containing methanol and 0.05% TFA as the mobile phase provides a distinct economic advantage and convenience compared to the preparation of acetonitrile and buffer solutions. Along with economic considerations, the method also demonstrated higher sensitivity and a shorter analysis time compared to previous HPLC studies, with a detection limit of 0.3 µg/mL and an analysis time of 4 minutes.[6,7,11,26]

As a result of the study, a UHPLC method with high sensitivity and a wide working range conducted in a short analysis time, was introduced into the literature as an alternative method for the quantification of SRT in standard solutions and pharmaceutical preparations. The developed method gave acceptable results in the validity tests of selectivity, linearity, sensitivity, accuracy, precision, analytical recovery, and stability parameters. The method has been successfully applied to pharmaceutical preparations. Thus, the UHPLC method proved to be applicable for the quantification of SRT in standard solutions and pharmaceutical preparations.

Ethics Committee Approval: Ethical approval and informed consent are not required in our study as no research was conducted on human or animal specimens.

Peer-review: Externally peer-reviewed.

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Declaration of Interests: The authors declare that they have no competing interest.

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