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Validated Spectrophotometric Methods for Determination of Rasagiline Mesylate in Pure and Dosage Forms Utilizing Charge Transfer Complexation Reaction

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Abstract
The current research focuses on creating and validating two straightforward, sensitive, precise, and cost-effective spectrophotometric techniques for detecting rasagiline mesylate (RSG) in its pure form and in pharmaceutical formulations. The methods rely on creating a charge transfer complex between RSG as the n-electron donor and either quinalizarin (Quinz) or alizarin red S (ARS) as the π-acceptor in methanol. This results in the formation of highly colored chromogens with absorption peaks at 565 nm for Quinz and 515 nm for ARS. The study examined the optimization of reaction parameters, including solvent type, reagent concentration, and reaction time.The stoichiometric ratio of the charge transfer complexes produced was determined to be 1:1 (RSG:reagent) using Job's method of continuous variation for both approaches. Beer's law is followed within the concentration ranges of 2.0–24 µg/ml using Quinz and 1.0–15 µg/ml using ARS under ideal conditions. This is supported by a high correlation coefficient ($r^2 \geq 0.9991$) and a low relative standard deviation (RSD% ≤ 0.90). The detection and quantification limits were determined to be 0.57 and 1.93 µg/ml for Quinz, and 0.28 and 0.93 µg/mL for ARS. The approaches were effectively used to determine RSG in its pharmaceutical formulations, and the validity was assessed using the usual addition procedure. The results obtained using the proposed approaches for the pure RSG and commercial tablets closely matched those obtained using the reported method.

Keywords
Rasagiline mesylate, Spectrophotometry, Charge transfer reaction, Quinalizarin, Alizarin red S, Dosage forms

INTRODUCTION

Rasagiline mesylate is chemically known as (1R)-2,3-dihydro-N-2-propynyl-1H-inden-1-amine (Figure 1). Rasagiline is a potent, specific, and irreversible second-generation monoamine oxidase inhibitor that targets the type B enzyme (MAO-B). The beneficial benefits observed in models of dopaminergic motor dysfunction treated with rasagiline are likely due to an increase in dopamine levels and enhanced dopaminergic activity. 1-Aminoindane is a potent primary metabolite and does not operate as an MAO-B inhibitor. Rasagiline is used to treat idiopathic Parkinson's disease either on its own (without levodopa) or in combination with levodopa for patients experiencing dosage-end fluctuations[1,2].

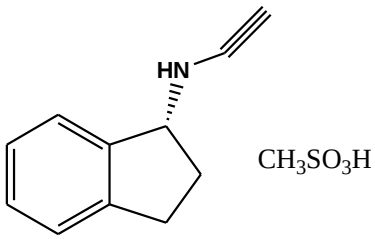

Fig. 1 The chemical structure of rasagiline mesylate (RSG)

The literature review showed many analytical techniques used to detect RSG in pharmaceuticals and biological fluids, such as chromatography[3-9], electrochemistry[10], and spectrophotometry[11-18]. As far as we know, there is no official monograph for rasagiline in any pharmacopoeia. The methodologies are intricate, necessitating extensive and arduous preparation of the materials and meticulous clean-up processes before analysis. Spectrophotometry is widely regarded as the most convenient analytical method in quality control labs, hospitals, and pharmaceutical businesses due to its simplicity, cheap cost, sensitivity, selectivity, accuracy, and precision. Alizarin derivatives have been utilized for the spectrophotometric analysis of some medicines[19-24].

This study introduces a straightforward, sensitive, quick, precise, and verified spectrophotometric technique for detecting RSG in its pure form and pharmaceutical products. The approach presented includes the creation of a charge transfer complex between RSG and two alizarin derivatives, quinalizarin (Quinz) and alizarin red S (ARS), acting as chromogenic reagents. The proposed approaches have been statistically validated for accuracy, precision, sensitivity, selectivity, robustness, and ruggedness according to ICH recommendations[25].

MATERIALS AND METHODS

Instrumentation

The absorption spectra were obtained using a Shimadzu UV-1601 UV/visible double beam spectrophotometer from Sweden, which was equipped with a 10 mm quartz cell for measuring absorbance. The spectrophotometer offers a wavelength accuracy of ±0.2 nm, a scanning speed of 200 nm/min, and a bandwidth of 2.0 nm within the wavelength range of 200–900 nm.

Materials and reagents

All chemicals, solvents, and reagents utilized in this study were of analytical reagent or pharmaceutical quality, and all solutions were freshly produced on a regular basis. A pure sample of RSG with a purity of 99.60 ± 1.0% was provided by Al Rowad Pharmaceutical Industrial Co. Cairo, Egypt. Dopaminct tablets contain 1 mg of RSG per tablet and are produced by Marcyrl-Pharmaceutical Industries, Cairo, Egypt. Parkintreat tablets contain 1 mg of RSG per tablet and are produced by Sedico/inspire pharmaceutical company, Cairo, Egypt.

Quinalizarin 1,2,5,8-tetrahydroxy-anthraquinone (Quinz) and alizarin red S, 3,4-dihydroxy-9, 10-dioxo-2-anthracene sulfonic acid (ARS) (Sigma-Aldrich) were used without further purification.

Preparation of standard solutions

Stock standard solutions of RSG were generated by dissolving a specific weight of pure RSG in methanol in a 100 ml measuring flask to achieve concentrations of 100 µg/ml and 1.0×10^{-3} mol/l. The standard solutions remained stable for a minimum of one week without any changes when stored in an amber-colored bottle and kept in a refrigerator when not being used. Serial dilution using the same solvent was conducted to achieve the desired concentration ranges.

Stock solutions of Quinz and ARS reagents were generated by dissolving the reagent in methanol to a concentration of 1.0×10^{-3} mol/l. The solution was then made up to 100 ml in a volumetric flask. The solutions remained stable for a minimum of one week when stored in the refrigerator.

General procedures

Portions of the standard RSG working solution were placed into 10 ml volumetric flasks within the concentration ranges of 2.0-24 µg/ml for Quinz and 1.0-15 µg/ml for ARS. Each flask received 2.0 ml of a solution containing 1.0×10^{-3} mol/l of Quinz or ARS. The mixture was agitated to facilitate the process, and methanol was added to reach the specified volume. The absorbance of the solutions was measured at 565 nm for Quinz and 515 nm for ARS, against reagent blanks made at the same time. A calibration graph was created by graphing the absorbance against the final concentration of RSG. The regression equation was determined.

Applications to pharmaceutical formulations

Twenty tablets were crushed, finely powdered, weighed, and the average weight of one tablet was established. The precise weight of the powdered tablets, which is equivalent to 5 mg of RSG, was dissolved in 10 ml of methanol. The solution was shaken for 5.0 minutes and then filtered using a Whatman No. 42 filter paper. The filtrate was diluted with methanol in a 50 ml measuring flask to create a 100 µg/mL stock solution for measurement using the suggested spectrophotometric techniques. Next, an appropriate portion was analyzed using the spectrophotometric methods mentioned earlier. Calculate the tablets' nominal content by applying the relevant regression equation from the calibration graphs.

Stoichiometric relationship

The stoichiometric ratios of the ion-associates generated between RSG and the reagents were calculated using the continuous variation method at the wavelengths where absorbance is highest. The continuous variation approach used equimolar solutions, specifically a 1.0×10^{-3} mol/l standard solution of RSG and a 1.0×10^{-3} mol/l solution of the reagent. Several solutions were created with a fixed total volume of 2.0 ml, containing RSG and the reagent. The medication and reagent were combined in different ratios ranging from 0:2 to 2:0, inclusive. The mixture was then made up to volume in a 10 ml calibrated flask using the suitable solvent as per the process indicated above. The absorbance of the solutions was measured at the ideal wavelength for each complex.

RESULTS AND DISCUSSION

Absorption Spectra

The suggested approach relies on the charge transfer reaction between RSG and Quinz or ARS in a methanolic solution, occurring in two phases. Optimizing experimental settings to produce optimum sensitivity and selectivity. This step involved assessing the impact of the solvent type, examining the effect of reagent concentration, determining the reaction time, and studying the reaction by evaluating stoichiometry using Job's continuous variation method, calculating the association constant and molar absorptivity in methanol, and confirming the proposed reaction mechanism. To obtain optimal sensitivity, the impact of chemical factors including solvent type, reagent concentration, and reaction time was assessed. The reaction was analyzed based on the stability of the product, its stoichiometry, and the resultant apparent molar absorptivity and association constant. The most favorable conditions for analyzing RSG were found in a methanol solution containing Quinz and ARS.

The radical anion was generated in the medium under ideal circumstances just after combining the reagents. It exhibited peak absorbance at 565 nm and 515 nm using Quinz and ARS, respectively, in a methanol medium (Figures 2 and 3). Therefore, these wavelengths were selected for all subsequent observations to achieve the best sensitivity for the proposed methodologies. The Quinz and ARS individually show peak absorbance at 491 nm and 421 nm in a methanol medium. The significant disparity in the absorbance bands' maxima of the reagent and product, which are 74 nm and 94 nm for Quinz and ARS, respectively, facilitated the accurate detection of the products while minimizing interference from the excess reagents present in the medium.

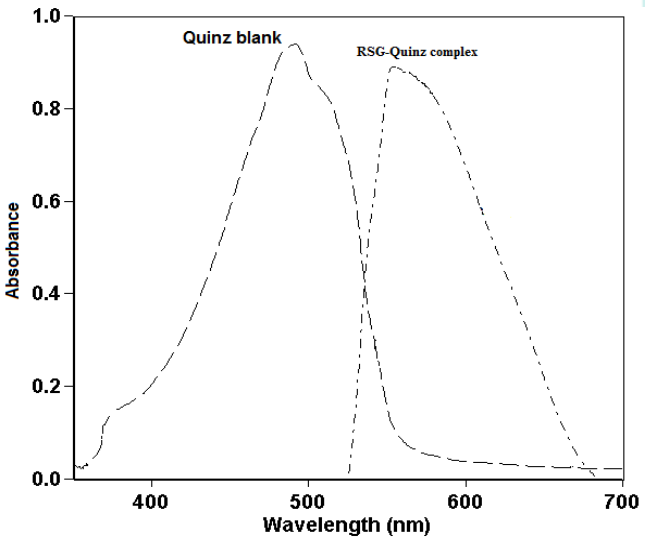

Fig. 2 Absorption spectra for the reaction product of (24 µg/ml) RSG against (1.0×10^{-3} mol/l) Quinz reagent blank solution

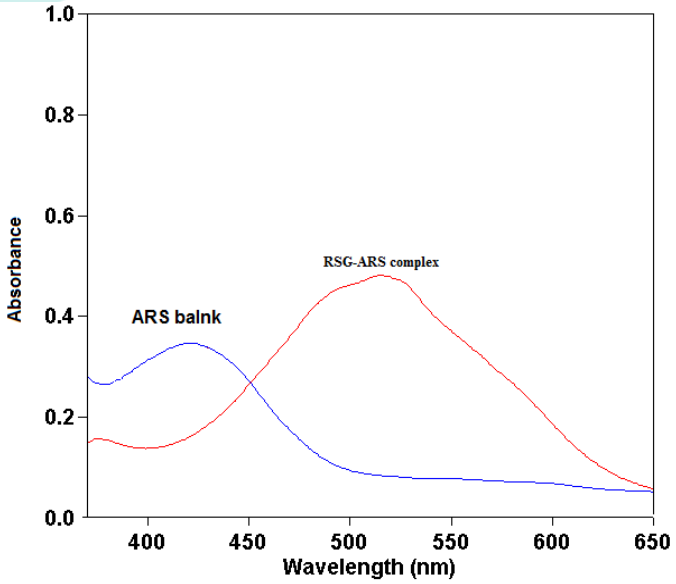

Fig. 3 Absorption spectra for the reaction product of (15 µg/ml) RSG against (1.0×10^{-3} mol/l) ARS reagent blank solution

Evaluation of the effect of the solvent nature

The solvent is crucial in charge transfer reactions since it needs to enable complete charge transfer, permit complicated dissociation, and stabilize the radical anion, which is the absorbing species. Solvents with a high dielectric constant are more effective for this task, as stated in the literature. Considering this fact, water would be a superb solvent for the technique. The low solubility of Quinz and ARS in water prevented their usage in this circumstance. The reaction was evaluated in ethanol, methanol, acetone, DMSO, and acetonitrile solvents. The maximum dielectric constant was found in DMSO and acetonitrile, while the best sensitivity was reached with methanol due to its ability to form stable hydrogen bonds with the radical anion. Methanol was selected for additional testing (Fig. 4).

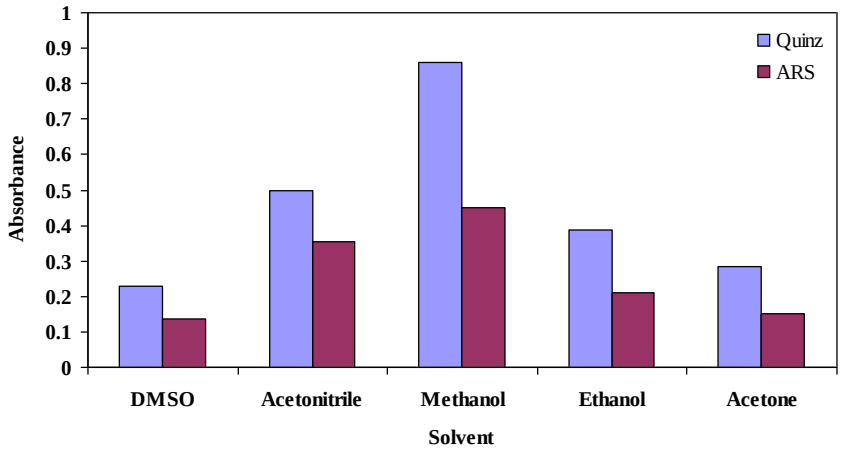

Fig. 4 Effect of different solvents on the charge transfer complex formation obtained against (1.0×10^{-3} mol/l) Quinz or ARS solutions also prepared in each solvent. RSG drug concentration; (24 and 15 µg/ml) for Quinz and ARS, respectively

Effect of reagents concentration

To achieve this goal, an experiment was conducted by altering the concentration of reagents within the range of 0.5-5.0 ml of (1.0×10^{-3} mol/l) Quinz and ARS solutions, while keeping the RSG concentration constant. A significant increase in absorbance was seen up to 2.0 ml of (1.0×10^{-3} mol/l) Quinz and ARS reagents. After this threshold, the absorbance remained steady (Figure 5). Hence, 2.0 ml of a solution containing 1.0×10^{-3} mol/l of Quinz and ARS reagents is the recommended volume for the reaction.

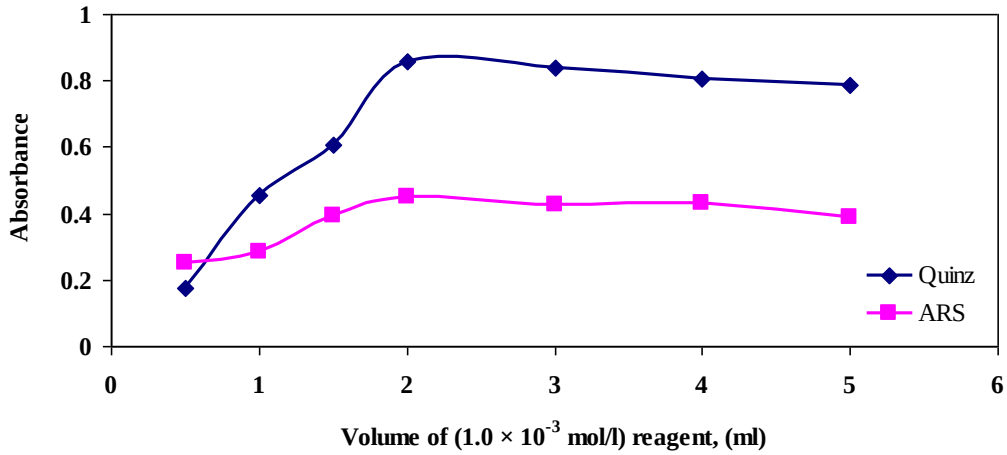

Fig. 5 Effect of (1.0×10^{-3} mol/l) reagent concentration on the absorbance of RSG-reagent complex. RSG concentration; (24 and 15 µg/ml) for Quinz and ARS, respectively

Effect of the reaction time

The ideal reaction time was determined by measuring the absorbance at specific wavelengths of an RSG solution with concentrations of 24 µg/ml and 15 µg/ml using Quinz and ARS reagents, respectively, at a laboratory temperature of 25±2°C. Color development and measurements were completed 5.0 minutes after combining RSG with the reagents. Increasing the temperature caused a drop in the absorbance of the charge transfer complex with a hypochromic shift, ultimately decaying at 40 °C.

Sequence of additions

The optimal order for adding the components is "RSG-reagent-solvent" to achieve full color development, maximum absorbance, and stability at the specified wavelength. Other sequences required more time as well as having lesser stability. These complexes maintain stability for a minimum of 10 hours. Following this period, absorbance experienced a minor decline.

Stoichiometric ratio

Job's continuous variation method was used to establish the stoichiometry of the charge transfer reaction in a methanol solution. Figure 6 demonstrates that the molar ratio resulting in the highest absorbance was determined to be 1:1 (RSG: reagent). Based on this outcome, a reaction mechanism was suggested involving the transfer of a free electron from the nitrogen atom in one molecule of RSG to the charge-deficient core of Quinz or ARS molecule, resulting in a total charge transfer.

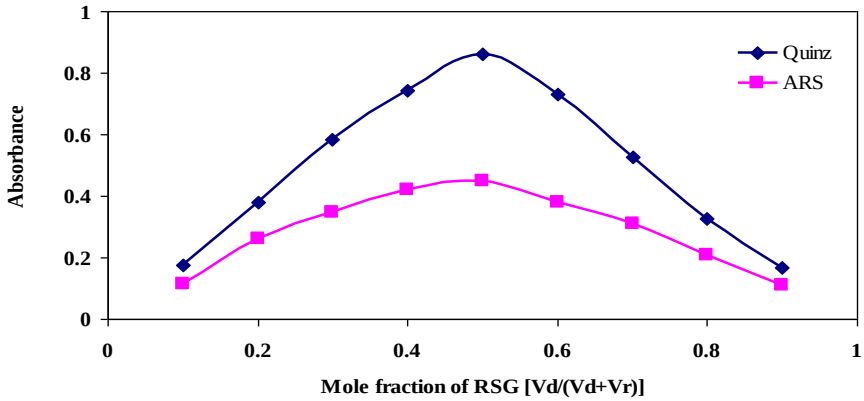

Fig. 6 Application of Job's method to the reaction between RSG and Quinz and ARS reagents

Method of validation

The proposed method was validated according to ICH guidelines[25] concerning linearity, sensitivity, accuracy, precision, limit of detection (LOD), limit of quantitation (LOQ), robustness and ruggedness.

Linearity

The absorbance-concentration relationship for the RSG medication was linear within the concentration ranges of 2.0–24 µg/ml using Quinz and 1.0–15 µg/ml using ARS under the specified experimental conditions.. The calibration graph is defined by the equation (A = a + b C), where A represents absorbance, an is the intercept, b is the slope, and C is the concentration in µg/ml. This equation is derived using the method of least squares. Table 1 summarizes the correlation coefficient, intercept, and slope for the calibration data. The Ringbom concentration range was determined by graphing the log concentration of the drug in µg/ml against transmittance %. The linear section of the curve provides an accurate microdetermination range for RSG, as shown in Table 1. The molar absorptivity of the colored charge transfer complexes and relative standard deviation were computed and published in Table 1.

Sensitivity

ICH guideline[25] outlines various methods for establishing the limits of detection (LOD) and quantitation (LOQ). These factors consist of visual assessment, signal-to-noise ratio, and the utilization of standard deviation of the response and the gradient of the calibration curve. The Limit of Detection (LOD) and Limit of Quantification (LOQ) of the method were established by injecting increasingly lower amounts of reference solutions using the devised technique. The Limit of Detection (LOD) and Limit of Quantification (LOQ) for the suggested approaches were determined using a specific equation[25, 27]:

$$LOD = 3s / k \text{ and } LOQ = 10\, s / k$$

where *s* is the standard deviation of ten replicate determinations values of the reagent blank or the standard deviation of intercepts of regression lines and k is the sensitivity, namely the slope of the calibration graph.

In accordance with the formula, LODs were found to be 0.57 and 0.28 µg/ml and LOQ were found to be 1.93 and 0.93 µg/mL using Quinz and ARS, respectively.

Table 1 Statistical analysis and analytical data in the determination of RSG using the proposed methods.

Parameters	Quinz	ARS
Beer's law limits, µg mL^{-1}	2.0–24	1.0-15
Ringboom limits, µg mL^{-1}	4.0-20	3.0-12
Molar absorptivity, x 10^4 L mol^{-1} cm^{-1}	2.412	1.659
Sandell sensitivity, ng cm^{-2}	11.08	16.11
Regression equation[a]		
Intercept (a)	-0.0046	-0.0003
Standard deviation of intercept (S_a)	0.008	0.005
Slope (b)	0.0191	0.0289
Standard deviation of slope (S_b)	0.013	0.028
Correlation coefficient, (r^2)	0.9991	0.9993
Mean ± SD [b]	99.80±0.70	99.20±0.90
RSD%	0.70	0.90
RE%	0.74	0.95
Limit of detection, µg mL^{-1}	0.57	0.28
Limit of quantification, µg mL^{-1}	1.93	0.93
Calculated *t*-value [c]	0.37	0.67
Calculated *F*-value [c]	2.04	1.23

[a] $A = a + bC$, where C is the concentration in µg/mL, A is the absorbance units, a is the intercept, b is the slope.

[b] SD, standard deviation; RSD%, percentage relative standard deviation; RE%, percentage relative error.

[c] The theoretical values of *t* and *F* at P= 0.05 are 2.571and 5.05, respectively, at confidence limit at 95% confidence level and five degrees of freedom (p= 0.05)

Accuracy and precision

The suggested method's accuracy was assessed by assessing three distinct concentrations of RSG within the linearity range in six replicates. Accuracy was quantified by recovery percentage and percent relative error (RE%) for RSG, while precision was assessed by relative standard deviation (RSD%). Intra-day precision was conducted on the same day, while inter-day precision was conducted on three different days (n=6 for each level). The findings of this inquiry are outlined in Table 2. The low values of the relative standard deviation (RSD%) and percentage relative error (RE%) suggest high precision and accuracy of the proposed approaches.

Table 2 Intra-day and Inter-day accuracy and precision data for RSG obtained by the proposed methods

Method	Taken concentration (µg/ml)	Recovery % [a]	Precision RSD % [a]	Accuracy RE % [a]	Confidence limit [b]
			Intra-day		
Quinz	5.0	99.30	0.50	-0.70	4.965 ± 0.026
	10	99.80	1.20	-0.20	9.98 ± 0.126
	15	100.30	1.40	0.30	15.045 ± 0.201
ARS	5.0	99.10	0.30	-0.90	4.955 ± 0.016
	10	100.80	0.65	0.80	10.08 ± 0.069
	15	99.50	1.10	-0.50	14.925 ± 0.172
			Inter-day		
Quinz	5.0	99.00	0.60	-1.0	4.95 ± 0.031
	10	99.90	0.95	-0.10	9.99 ± 0.10
	15	98.80	1.50	-1.20	14.82 ± 0.233
ARS	5.0	100.20	0.70	0.20	5.01 ± 0.037
	10	99.40	1.30	-0.60	9.94 ±0.136
	15	99.70	1.70	-0.30	14.955 ± 0.267

[a] Mean±standard error (n=6), RSD%, percentage relative standard deviation; RE%, percentage relative error

[b] Confidence limit at 95% confidence level and five degrees of freedom (t = 2.571)

Robustness and ruggedness

Robustness was examined by evaluating the influence of small variation of method variables, including concentration of reagents and reaction time on the performance of the proposed methods. The analysis was performed with altered conditions by taking three different concentrations of RSG and it was found that small variation of method variables did not significantly affect the procedures as shown by the RSD% values in the range of 0.50-2.40 %. This provided an indication for the reliability of the proposed methods during its routine application for the analysis of RSG and so the proposed spectrophotometric methods are considered robust.

Methods ruggedness was expressed as the RSD% and was also tested by applying the proposed methods to the assay of RSG using the same operational conditions but using three different instruments as well as three different anaysts. The inter-analysts RSD% were in the range 0.65-2.10%, whereas the inter-instruments RSD% ranged from 0.70-2.50% suggesting that the developed methods were rugged. The results are shown in Table 3.

Table 3 Results of methods robustness and ruggedness (all values in RSD%) studies

Methods	Nominal concentration (µg/ml)	RSD%			
		Robustness		Ruggedness	
		Variable alerted [a]			
		Reagent volume (n=3)	Reaction time (n=3)	Different analysts (n=3)	Different instruments (n=3)
Quinz	5.0	1.30	0.55	0.70	0.70
	10	1.70	0.85	1.80	1.60
	15	2.40	2.0	2.10	2.40
ARS	5.0	0.50	0.90	0.65	0.80
	10	0.85	1.30	1.20	1.50
	15	1.70	2.10	2.10	2.50

[a] Volume of (1.0×10^{-3} mol/l) reagent is (2.0±0.2 mL) and reaction time is (5.0±1.0 min) (after adding reagent) were used

Recovery studies

A recovery experiment was conducted using the usual addition methodology to determine the accuracy, reliability, and validity of the proposed methodologies. The investigation involved adding three varying concentrations of pure RSG (50%, 100%, and 150% of the tablet's RSG level) to a set quantity of tablet powder containing the drug. The total concentration was then determined using the suggested techniques. The experiment involved repeating the determination at each level three times and then calculating the percentage recovery of the added standard using the formula:

$$\% \text{ Recovery} = ([C_F - C_T]) / C_p \times 10$$

where C_F represents the total concentration of the analyte found, C_T is the concentration of the analyte in the tablet preparation, and C_P is a concentration of the analyte (pure drug) given to tablet preparations. The study's findings, as shown in Table 4, demonstrated that the accuracy of the suggested methodologies remained consistent regardless of the different excipients found in the tablets, which did not disrupt the analysis.

Table 4 Results of recovery experiments by standard addition method for the determination of RSG in tablets using the proposed methods and statistical comparison with the reported method[16]

Samples	Taken drug in tablet (µg/ml)	Pure drug Added (µg/ml)	Dopaminct tablets		Parkintreat tablets		Reported method[16]
			Total found (µg/ml)	Recovery [a] (%) ± SD	Total found (µg/ml)	Recovery [a] (%) ± SD	
	8.0	4.0	11.94	99.50 ± 0.27	11.856	98.80 ± 0.20	
Quinz	8.0	8.0	15.792	98.70 ± 0.36	15.888	99.30 ± 0.48	
	8.0	12	19.82	99.10 ± 0.58	20.12	100.60± 0.67	
Mean recovery % ± SD				99.10±0.40		99.57±0.93	99.60±0.80
RSD%				0.40		0.93	0.80
Variance				0.16		0.86	0.64
t-value [b]				1.25		0.05	
F-value [b]				4.0		1.43	
	6.0	3.0	8.946	99.40 ± 0.21	8.91	99.00 ± 0.15	
ARS	6.0	6.0	12.084	100.70± 0.29	11.976	99.90 ± 0.40	
	6.0	9.0	15.225	101.0± 0.45	14.91	99.40 ± 0.60	
Mean recovery % ± SD				100.37±0.85		99.43±0.45	100.10±0.86
RSD%				0.85		0.45	0.86
Variance				0.72		0.20	0.74
t-value [b]				0.50		1.54	
F-value [b]				1.03		3.70	

[a] Average of six determinations
[b] The theoretical values of t and F are 2.571 and 5.05, respectively at confidence limit at 95% confidence level and five degrees of freedom (p = 0.05)

Analysis of pharmaceutical formulations

The suggested techniques were used to measure RSG in pharmaceutical formulations. Table 4 presents a statistical comparison of the accuracy and precision between the findings obtained from the assay of RSG using the proposed methods and the reported method16. Statistical comparison between the results and the official technique was conducted using Student's t-test for accuracy and F-test for precision. The estimated *t*-value and *F*-value at a 95% confidence level did not surpass the tabular values for five degrees of freedom. Therefore, there is no statistically significant difference between the proposed approaches and the reported method in terms of accuracy and precision at a 95% confidence level.

CONCLUSIONS

This study explores the use of charge transfer complexation reaction involving two alizarin derivatives to measure rasagiline mesylate (RSG) in its pure form and in pharmaceutical products. The proposed approaches are simpler, faster, more cost-effective, sensitive, accurate, and resilient for determining RSG in its pure form and pharmaceutical formulations compared to the current spectrophotometric method. Additionally, the suggested techniques eliminate laborious experimental procedures including extraction, heating, and pH modification. These approaches are appealing because they are relatively free from influence by common diluents and excipients present in higher levels than usual in pharmaceutical formulations. The statistical metrics and recovery data demonstrate the approaches' high accuracy and precision. Hence, the validated methodologies proposed could be beneficial for the regular quality control analysis of RSG in its pure form and pharmaceutical product

CONFLICTS OF INTERESTS

The authors confirm that this article content has no conflict of interest.

AUTHOR'S CONTRIBUTIONS

Prof. Dr. Alaa E. Ali has generated the research idea and interpreted the data and helped to draft the manuscript. Prof. Dr. Ayman A. Gouda helped in check spelling, reducing the plagiarism, interpreting the data, reviewed the manuscript and submit the manuscript for publication. Dr. Ragab Y. Sharaf carried out the experiments, and participated in the design of the study. Miss. Basant S. Emam was prepared the solutions, carried out the experiments, interpreted the data and helped to draft the manuscript. Dr. Gehan S. Elasala helping in carrying out the experiments, and participated in the design of the study.

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