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Development and Validation of Spectrophotometric Method for Determination of Riluzole in its Dosage Form using Phloroglucinol as coupling Agent

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ABSTRACT

The goal of the present study was to create and validate a newly developed, quick, precise, and easy-to-use spectrophotometric technique for identifying substances with amino group in pure and in pharmaceutical formulations, particularly riluzole. Two steps are involved in the suggested procedure: first, diazotization of riluzole's primary amine with sodium nitrite in an acidic medium to form riluzole diazonium salt; second, reacting the diazonium salt with reagent in a basic medium to produce a stable purple-red water-insoluble dye with maximum absorption at 530 nm. As a result, the resulting azo dye satisfies Lambert's law within a concentration range of 20 – 50 mg/L. The method was tested for linearity, precision, accuracy, and limits of quantification and detection. It was also optimized for several production variables. The results confirmed the statistical validity of the methodology with a molar absorptivity of 6.8443 $\times 10^{+3}$ L.mol^{-1}. cm^{-1} and a Sandell's sensitivity of 0.0227 mg. L^{-1}/0.001 abs. unit. .In overall, the findings indicate which this approach succeeds well for routinely measuring riluzole in quality control procedures involving both pure and tablet formulations.

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1. INTRODUCTION

As 2-amino-6-(trifluoromethoxy)benzothiazole, or riluzole (RLZ), is generated from benzothiazole (Fig. 1) [1]. Its chemical formula is $C_8H_5F_3N_2OS$, and its molecular weight is 234.198 g/mol. A number of methods have been documented for detecting RLZ in various samples, such as liquid chromatography in mouse plasma[2], liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) in beagle dogs' plasma[3], Riluzole concentrations in serum and plasma are determined using a validated High-Performance Liquid Chromatography (HPLC) technique [4], in human plasma through Liquid Chromatography-Tandem Mass Spectrometry Method[5] or liquid chromatography-electrospray ionization tandem mass spectrometry [6] or UPLC-MS/MS method[7], and in rat brain using high-performance liquid chromatography and spectrophotometry [8]. To identify riluzole in the presence of alkaline and oxidative degradation products, a validated reversed-phase HPLC test has been created, promising stability indication [9]. Furthermore, spectrophotometric techniques[10-12], as well as other analytical approaches such as densitometric analyses [13], stability-indicating high-performance liquid chromatography (HPLC) methods [14-16], as well as electrochemical and voltammetric analyses[17] , have been reported for identifying RLZ in bulk dose tablet formulations.

RLZ is among the approved treatments for amyotrophic lateral sclerosis[18]. Its mechanism of action is intricate and involves enhancing glutamatergic neurotransmission[19]. Recent studies have highlighted the potential of RLZ as an antiproliferative agent against various cancers, including skin, breast, pancreas, colon, liver, bone, brain, lung, and nasopharynx[20]. Notably, RLZ's ability to cross the blood-brain barrier positions it as a promising option for glioma treatment [21, 22], and for managing brain metastasis in advanced melanoma [23]. As a derivative of benzothiazole, RLZ holds promise as an anti-amoebic agent against Entamoeba histolytica [24]. The goal of the present investigation is to establish and confirm a new technique for measuring RLZ in tablet and pure form spectrophotometrically by using phloroglucinol as a chromogenic coupling reagent for the diazo process.

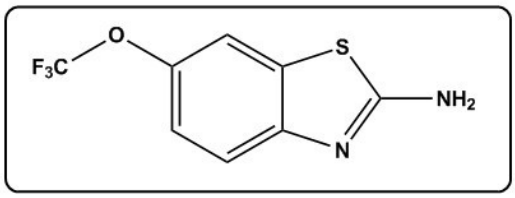


Figure 1: Riluzole, or 2-amino-6-trifluoromethoxy-benzothiazole, as in its chemical form.

2. EXPERIMENTAL METHODOLOGY.

2.1. Experimental materials and equipment

A CECIL 7200 UV-Visible double beam spectrophotometer was used for spectrophotometry, recording absorption spectra with quartz cells that were matched to a distance of 1 cm. Three other instruments were a Jenway hot plate magnetic stirrer, a DelLab®/DLA-PH digital pH meter, and a Shimatzu/AUY220 analytical balance. Every chemical and reagent used was of the analytical variety. Local suppliers provided 50 mg film-coated Rilutek® riluzole tablets; Fluka supplied sodium hydroxide (NaOH) and sulfamic acid (H_3NSO_3); Synth® supplied 37% hydrochloric acid; BDH supplied sodium nitrite; Sigma-Aldrich supplied pure riluzole and 98% pure phloroglucinol; and a variety of suppliers provided KOH, C_2H_5OH, HCl, HNO_3, $NaHCO_3$, CH_3COOH, and H_2SO_4. The solutions were made in the manner described below:

A 0.1 g of authentic, pure RLZ was dispersed into 15 mL of absolute ethanol to create a standard 1000 ppm (mg/L) RLZ substance solution in a 100-mL volumetric container filled with distilled water (DW). Additionally, 0.25 g of phloroglucinol was dissolved in 10 ml of DW to produce a solution with a (0.02 mol. L^{-1}), which was then transferred to a volumetric container with a capacity 100 mL filled with DW. Furthermore, a 2% Sodium Nitrite Solution (w/v), it was prepared by dissolving 2.0 g of $NaNO_2$ in DW, transferring the mixture to a 100 milliliter volumetric flask, and filling it with DW. Moreover, hydrochloric acid solution (2M), it was produced by diluting 3.3 ml of concentrated HCl 37% to the appropriate amount in a 20 mL volumetric flask with same solvent (DW). In addition, a sodium hydroxide solution (2M), (SH) was prepared by dissolving 8.0 g of NaOH in a small amount of DW in a 100 mL volumetric flask and then diluting it to the proper amount with same solvent. Lastly, a 2% w/v sulfamic acid solution (SA) was created by dissolving 2.0 g of pure SA in DW and transferring it to a 100 mL volumetric flask filled with DW.

2.2. Recommended Procedure and Preparation of the Calibration Curve

Based on optimal conditions derived from various studies, 1 to 2.5 mL of the standard RLZ drug solution (1000 mg/L) was pipetted out and diluted to 50 ml in volumetric flasks to produce solutions containing 20 to 50 mg/L of pure RLZ. Subsequently, 2 mL of 2M HC solution, 3 ml of 2% w/v SN solution, and then 1.5 ml of 2% w/v SA solution were added to each flask. The reaction mixtures were mixed thoroughly for 5 minutes, cooled in an ice bath for 2–5 minutes, shaken, and allowed to stand for 5 minutes. Next, 0.5 ml of phloroglucinol (0.02 M) and 1.5 ml of 2 M SH solutions were introduced, and the mixture was allowed to stand for 10 minutes. After completely mixing and diluting each flask's contents with DW to the appropriate level, the absorbance (A at 530 nm) spectra of each flask solution were examined in comparison with the blank solution, which was prepared in the same way but did not include RLZ at 530 nm using quartz cells that measured one centimeter.

2.3. Procedure for preparing riluzole tablet solution

Ten tablets of 50 mg film-coated Rilutek® riluzole tablets were weighed, crushed into a fine powder, and a precisely measured amount of powder equal to 0.1 g of RLZ tablet was dissolved in 10 ml of absolute ethanol. This solution was then transferred to a 100-ml volumetric flask and diluted with DW to the mark to create a stock solution with a concentration of 1000 ppm (mg/L).

Subsequently, 1.25 ml and 1.75 ml of the stock solution were pipetted and transferred into two 50-ml volumetric flasks to create standard solutions A and B, with concentrations of 25 mg/L and 35 mg/L, respectively. The same recommended procedure was applied to film-coated 50 mg riluzole tablets to prepare sample solutions A and B. The absorbance (A at 530 nm) of the standard and sample solutions (A and B) was determined at a wavelength of 530.0 nm, using a blank solution, a solution without the analyte.

2.4. Experiments aimed at determining the optimal reaction conditions

In the quest to determine the best reaction conditions for RLZ identification, various factors influencing the color development of azo dye were examined. Optimization involved altering each parameter independently while holding the rest constant. Tables 1–9 showcase test outcomes selected for their vibrant color intensity and low reagent blank absorbance. The experiment utilized 50 mg/ 50 mL of riluzole in a 50-ml solution. Key findings included:

1. Reagent Volume: 0.5 mL of reagent was found to be the optimal volume for achieving the highest Absorbance intensity (Table 1).
2. Base Effects: Strong bases like 2M sodium hydroxide (NaOH) with 1.5 mL provided the best results in terms of color contrast, intensity, and stability of the yellow azo dye (Table 2). Weaker bases like sodium bicarbonate produced color formation but with a slower reaction time.
3. Sodium Nitrite: A volume of 3 mL of 2% sodium nitrite solution ($NaNO_2$) was determined to be necessary for achieving a consistent and maximum color intensity of the azo dye complex (Table 3).
4. Acid Type: Hydrochloric acid (HCl) was found to be the most effective acid for the diazotization reaction due to its stability and ability to produce the highest absorbance values compared to sulfuric acid (H_2SO_4), nitric acid (HNO_3), and acetic acid (CH_3COOH) (Table 4).
5. Acidity Volume: 2.0 mL of 2 M HCl was identified as the optimal volume for the diazotization process, resulting in the highest and most consistent absorbance intensities (Table 5).
6. Sulfamic Acid: The addition of 1.5 mL of a 2% w/v sulfamic acid solution yielded the greatest absorbance value. This suggests that this amount is most effective in eliminating excess nitrite ions (Table 6).
7. Coupling Reaction Time: After 10 minutes at room temperature, the color development of the azo dye reached its maximum intensity and remained stable for at least 60 minutes (Table 7).
8. Diazotization Reaction Time: The diazotization reaction was found to be very fast, with maximum absorbance at 530 nm occurring instantaneously (Table 8). No significant increase in Absorbance was observed beyond the initial formation of the colored product.
9. Effect of reagents mixing order: The investigation of the effects of varying component addition orders on azo dye production involved introducing reactants in four distinct orders, as indicated in table (9). Given that the third mixing order produced the highest absorbance at 530 nm, it is clear from the data that this order should be followed in the next tests.

Table 1: Effect of coupling reagent amount.

Volume (ml) of reagent	A at 530 nm
0.3	0.89
0.5	1.2
0.7	0.98
0.9	0.82
0.11	0.67
0.14	0.49

Table 2: Effects of the type of base and its amount on the estimation of RLZ.

Base solution	A at 530 nm / ml of 2 M base added									
	pH	1	pH	1.5	pH	2	pH	2.5	pH	3
NaOH	11.3	0.748	11.6	0.78	11.7	0.76	11.8	0.765	11.87	0.755
KOH	11.8	0.734	11.8	0.725	11.9	0.741	12	0.738	12	0.74
NaHCO	10.5	0.366	10.7	0.441	10.9	0.602	10.9	0.67	11.1	0.69

Table 3: Effect of 2% w/v $NaNO_2$ amount.

2% w/v NaNO2/ mL	A at 530 nm
1	0.37
1.5	0.56
2	0.66
2.5	0.67
3	0.69
3.5	0.53

Table 4: Effect of diazotization acids on the estimation of (50 ppm (mg/L)) RLZ.

Acidic solution with 2M	A at 530 nm / mL of acid used
CH3COOH	0.298
HNO3	0.512
H2SO4	0.558
HCl	0.623

Table 5: Effect of HCl (2 M) amounts.

Volume (mL) of HCl	A at 530 nm
0.5	0.23
1	0.31
1.5	0.34
2	0.4
2.5	0.29

Table 6: Effect of 2% w/v sulfamic acid amounts.

Volume (mL) of sulfamic acid	A at 530 nm
0.1	0.31
0.5	0.35
1	0.35
1.5	0.42
2	0.38

Table 7: Effect of coupling reaction time.

Time (min)	A at 530 nm
0	0.626
10	1.02
20	1.023
30	1.02
40	1.029
50	1.027
60	1.021

Table 8: Effect of diazotization reaction time.

Time (min)	A at 530 nm
0	0.523
5	0.66
10	0.69
15	0.65
20	0.67

Table 9: Variation of Absorbance at 530 nm with change of reactants addition order in the estimation of 50 $\mu g.mL^{-1}$ (RLZ).

No.	Sequence	A at 530 nm
1	R+D+S+H	1.02
2	D+R+S+H	1.26
3	D+S+R+H	1.42
4	R+S+H+D	0.87

D: riluzole R: phloroglucinol S: sodium nitrite H: sodium hydroxide

3. RESULTS AND DISCUSSION

3.1. Final Absorption Spectrum

The primary experiment for the above method involved diazotizing (RLZ) by react RLZ with sodium nitrite in an acidic medium. After that, the end product turned purple-red color when it reacted with phloroglucinol as a coupling reagent in an alkaline solution. The experiment was conducted by adding 2.5 mL of 1000 mg/L (RLZ.), 1.5 ml of 2% w/v sodium nitrite, 1 mL of 2 M HCl, 0.5 mL of 2 w/v sulfamic acid, 1 mL of reagent (phloroglucinol), and 3 mL of 2 M NaOH to a 50-milliliter volumetric container. After that, the mixture was shook. The contents were diluted to the proper amount using distilled water. The λmax of the colored product was ascertained by contrasting it with the reagent blank. Riluzole derivative azodye shows a maximum absorption at 530 nm, while the reagent blank shows no absorption at this wavelength. Figure 2 shows the absorption spectra.

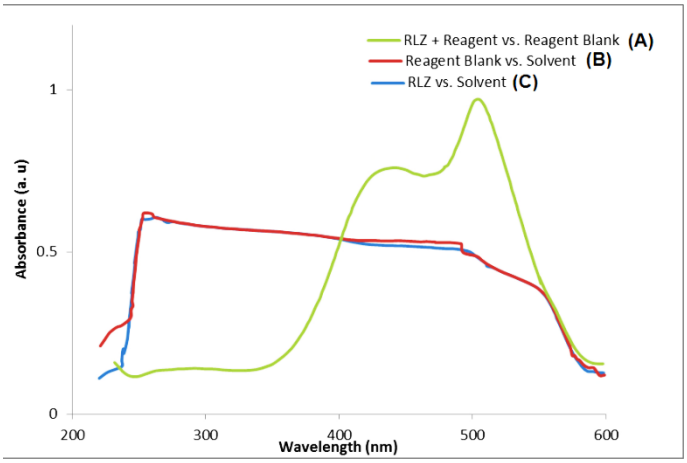


Figure 2: Absorption spectra of 50 µg/ 50 mL Riluzole-Phloroglucinol against reagent blank (A), reagent blank against solvent (B), and RLZ vs. solvent (C).

3.2. Calibration graph and analytical data

Plot the Absorbance (A at 530 nm) vs. concentration graph shown in Figure 3, which depicts the readings from Table 10, using the data obtained by following the suggested procedure. The acquired analytical parameters are displayed in Table 11, as per the ICH guidelines for the validation of analytical methods[25].

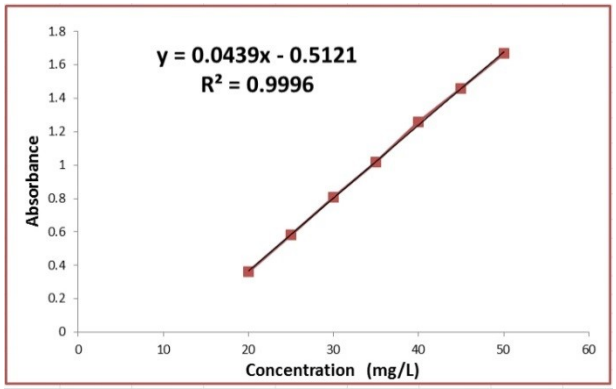


Figure 3: Standard calibration curve for RLZ via ideal condition calculation.

Table 10: The calibration curve data for the estimation of RLZ.

S. No.	Concentration of RLZ (mg/L)	A at 530 nm
1	20	0.36
2	25	0.58
3	30	0.81
4	35	1.02
5	40	1.26
6	45	1.46
7	50	1.67

Table 11: Optical and validation characteristics of proposed method

Parameters		Values
Beer's law limit (mg/L)		20 - 50
λmax (nm)		530
Color		Purple to red
Regression equation (y=a+bc)	Slope, b (L/mg)	0.0439
	Intercept, a (a=y-bc)	0.5121
Correlation coefficient (r^2)		0.9996
Precision expressed as % RSD	Intra-day	0.23
	Inter-day	0.46
Accuracy (recovery %)		99 >
LOD (mg/L)		2.8
LOQ (mg/L)		8.5
Sandell's sensitivity (mg. L-1/0.001 abs. unit)		0.022
Molar absorptivity (M-1. cm-1)		6.8443 ×10+3

y = b + ac, where c is the concentration in ppm (mg/L) and y is A at 530 nm.
A at 530 nm: Absorbance reading at 530 nm.
LOD and LOQ were determined using mathematical equations.
LOD= (3.3× SD)/S, and LOQ= (10× SD)/S.
Where, (SD) is a standard deviation of Y- intercept, and (S) is the slope of calibration curve.

3.3. Validation and Analytical Application of the Proposed Approach

The spectrophotometric method for estimating RLZ was validated across multiple parameters, including:

1- Precision

Intraday and inter-day investigations were carried out to show the precision of the analytical technique used to measure the concentration. Three distinct solutions were made and examined, all of which had the same concentration (50 mg/L). For the intra-day variation, absorbance at 530 nm was measured three times daily; for the inter-day variation, it was measured three times over three days. Table 12 displays the findings, which are given as a percentage of relative standard deviation, or % RSD.

Table 12: Intra-day and inter-day precision data

Declared con. (mg/L)	Intra-day precision Data		Inter-day precision Data	
	Con. Found (mg/L)	Precision (% RSD)	Con. Found (mg/L)	Precision (% RSD)
50	50.1	0.23	49.69	0.46
	49.87		50.13	
	49.94		50.04	

2- Accuracy

The accuracy of the proposed method was assessed by recovery studies using the standard addition method. A known quantity of riluzole (5 mg/L) from the dosage form was mixed with a pure standard drug solution at three distinct concentrations (20, 30, and 40) mg/L. The resulting solutions were then reanalyzed by the proposed method, and the percentage recovery was determined as described in Table 13.

Table 13: Results of recovery study for RLZ.

Conc. Of STD (mg/L) added	Conc. of sample mg/L	A at 530 nm	Total conc. mg/L	Recovery of STD	Recover of STD %
20	5	0.589	25.1	20.1	100.5
30	5	1.019	34.88	29.88	99.6
40	5	1.459	44.92	39.92	99.8

3- Linearity

In the developed UV method, various aliquots were prepared from the standard work solution (1000 ppm (mg/L)) ranging from 20 to 50 mg/L, and the samples were scanned in a UV-VIS spectrophotometer at a wavelength of 530 nm. It was found that the calibration curve was linear in the range from 20 to 50 mg/L, and another result is reported in Table 2. The proposed technique was carried out to quantify the amount of RLZ in 50 mg film-coated riluzole tablets that were purchased from the local market by following the suggested procedure that was described in the experimental section.

There were two different concentrations used: 25 and 35 mg/L. The A at 530 nm of the sample solutions was measured at a wavelength of 530.0 nm, with a solution without analyte used as the reference solution. The results are presented in table 14, and the amount of riluzole (RLZ) in each tablet was determined to be 50 mg/tablet.

Table 14: Assay of the marketed formulation

Name of drug	Label claim	Concentration prepared (mg/L)	Amount found (mg/L)	% Assay
Riluzole	50 mg	25	25.09	100.3
		35	35.98	99.95

3.4. The nature of the dye-azo product.

The stoichiometry of the azo dye was examined under the given conditions using the mole-ratio method[26]. The purple-red dye was produced by combining 1:1 diazotized riluzole with phloroglucinol, as per the experimental data technique (Figure 4). The dye may therefore have the suggested structure seen in Figure 5.

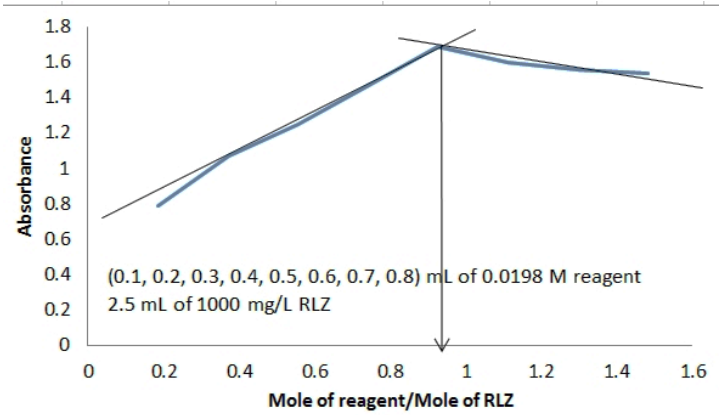


Fig. 4: Plot of the mole-ratio method.

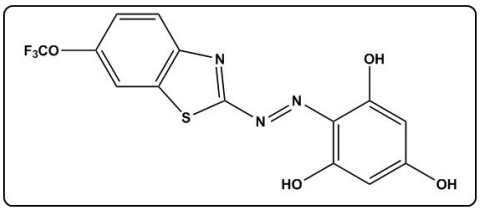
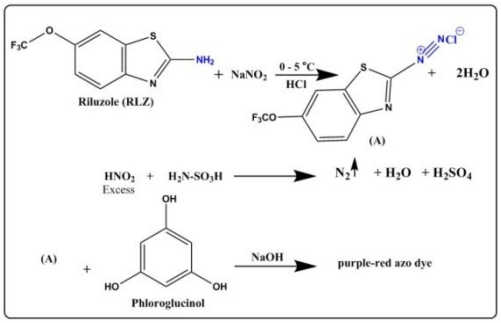


Figure 5: Suggested chemical structure of azo dye.

3.5. Path of the Reaction

Scheme 1 indicates that the current experiment is expected to follow the proposed reaction process between diazotized riluzole and phloroglucinol as a coupling reagent.



Scheme 1: The reactions suggested mechanism.

3.6. Comparing various approaches

The analysis variables from the present approach are compared with those from the current spectrophotometric method in Table 15.

Table 15: The comparison of the methods.

Analytical parameters	Present method	Literature method [12]
pH	11.6	9.2
λ max (nm)	530	225
Medium or reaction	Ethanol : Water	Alkaline
Correlation co-efficient (r^2)	0.9996	0.9984
Reagent	Phloroglucinol	Solubilizing agent
Beers law rang (mg/L)	20 – 50	1-5
Molar absorptivity (L. $mol^{-1}.cm^{-1}$)	6.8443 $\times 10^{+3}$	2.48 $\times 10^{+5}$
Colour of dye	Purple to red	-
Nature of dye	1:1	-
Type of reaction	Diazotisation and coupling	-
Application of method	Pharmaceutical preparations	Pharmaceutical preparations

3.7. Discussion

The proposed method seems to be able to detect the compound RLZ in its dose form with applicable analytical qualities. An excellent linear connection between absorbance (A at 530 nm) and concentration (mg/L) throughout the 20–50 mg/L range is demonstrated by Table 11, which aligns with Beer's law. The method is noteworthy for its ability to detect and quantify at low concentrations, as evidenced by its low limit of detection (LOD) of 2.81 mg/L and low limit of quantification (LOQ) of 8.52 mg/L. The obtained data demonstrated very near-100% mean recovery percent values (100.5, 99.6, and 99.8) for the successive concentrations of (20, 30, and 40) mg/L, respectively. These results, therefore, show that the suggested analytical procedures have a high degree of accuracy. The approach also shows low relative standard deviation (RSD) values of 0.23% intra -day and 0.46 % inter-day.

4. CONCLUSSION

Two novel, simple, sensitive, and cost-effective spectrophotometric methods for riluzole determination were successfully developed and optimized. These methods, based on both diazonium coupling reactions and CPE, demonstrated excellent applicability for quantifying trace and ultra-trace amounts of riluzole in pure and pharmaceutical formulations. The proposed method utilizing the coupling reaction of diazo riluzole with phloroglucinol in a basic medium proved particularly effective. This method offers high product stability, sensitivity, and provides accurate and reliable results without requiring solvent extraction or separation steps. Ultimately, this research introduces a valuable new spectrophotometric technique for riluzole analysis in both pure and tablet forms, employing phloroglucinol as a chromogenic coupling agent.

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