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# Assessment of Pseudoephedrine Sulfate by Spectrofluorometric Method in Pharmaceutical Formulations By means of Derivatization 2-Chloro-7-Nitrobenzo -2-Oxa-1, 3-Diazole

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**Abstract**

To identify a sympathomimetic medication, pseudoephedrine hydrochloride, a novel, profoundly delicate, and explicit spectrofluorometric technique has been devised. The current technique produced a highly luminous product that was measured at 532 nm (excitation at 475 nm) by derivatization with 2-Chloro-7-Nitrobenzo -2-Oxa-1, 3-Diazole in phosphate buffer at pH 7.8. The fluorescence intensity and pseudoephedrine hydrochloride concentration were shown to have a linear relationship and strong correlation at optimal conditions, ranging from 0.5 to 5 $mg/mL^{-1}$. The suggested approach was effectively used to test for pseudoephedrine hydrochloride in commercial pharmaceutical formulations with high precision and accuracy, free from common additive interference. A statistical analysis of the data using a recognized methodology revealed good agreement and demonstrated that the accuracy and precision did not differ significantly. The reaction's stoichiometry was established, and the reaction route was hypothesized.

**Keywords**: 2-Chloro-7-Nitrobenzo -2-Oxa-1, 3-Diazole, sympathomimetic, pseudoephedrine hydrochloride

## Introduction

As a sympathomimetic diastereomer of ephedrine, pseudoephedrine has the ability to decongest. In presynaptic neurons, pseudoephedrine sulfate (PSES) bis-((1S,2S)-2-(methylamino)-1-phenylpropan-1-ol); sulfuric acid displaces norepinephrine from storage vesicles and releases it into the neuronal synapses. The main receptors that are activated by this discharge are alpha-adrenergic receptors [1,2]. Its minimal direct agonist activity is also found at alpha- and beta-adrenergic receptors. Receptor-induced vasoconstriction eases congestion in the sinuses and nasal passages. Therefore, it is used to temporarily reduce sinus pressure, congestion, and pain caused by infections (like the flu or the common cold) or other respiratory disorders (such hay fever, allergies, or bronchitis) [3]. There are two derivatives from salts of

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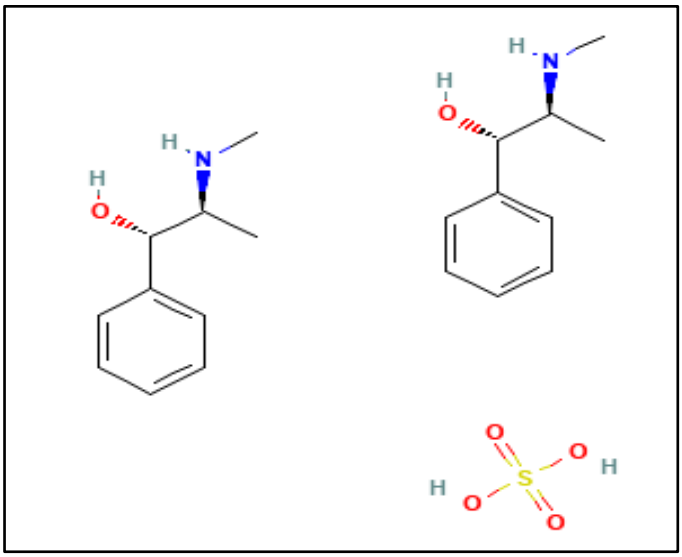
Pseudoephedrine (Pseudoephedrine sulfate and pseudoephedrine Hydrochloride) that have biological activity as drugs. It is frequently used, either alone or in conjunction with other medications, as a nasal and bronchi decongestant to treat respiratory allergies, sinusitis, hay fever, bronchitis, and the common cold [4,5].

Pseudoephedrine is categorized as a sympathomimetic amine that acts both directly and indirectly [6]. For the purpose of determining PSES in biological samples and pharmaceutical preparations, in recent years, methods based on spectrophotometry, derivative spectrophotometry, electrophoresis, gas chromatography, liquid chromatography, potentiometric and HPLC have been reported [7,8]. The majority of these techniques are costly and require time-consuming sample pre-treatments. 4-Chloro-7-nitrobenzofurazan (NBD-Cl) has been employed in the investigation of several medicinal substances as a fluorescent labeling reagent and as a reactivity probe [9,10]. As far as we are aware, no spectrofluorometric assay for pseudoephedrine hydrochloride has been reported. Using (NBD-Cl), a highly selective and sensitive reagent for primary and secondary amines, to derivative PSEH in order to detect it using a novel, sensitive, and precise spectrofluorometric method, was the goal of the current work. PSEH in pharmaceutical formulations was determined in order to assess the proposed method's applicability [9].



Scheme 1. Chemical structure of Pseudoephedrine sulfate

**Materials and methods**

**Sample and solutions preparation**

The governmental company for the pharmaceutical sector and medical appliances, SDI, Iraq, generously provided pseudoephedrine sulphate. Pharmaceutical preparations, such as Decongests SR capsules, syrup and drop (SDI, Iraq), were labeled to contain PSES in 0.8 mL and to include 5, 7.5, 10, and 120 mg apiece. The source of 2-chloro-7-nitrobenzo-2-oxa-1-3-diazole compound was from the well-known company Sigma Aldrich Chemical Co. (St. Louis,

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MO, USA). The remaining ingredients and solvents were all analytical grade from Bayouni Exclusive agent for the company Sigma Aldrich Chemical (Baghdad, Iraq).

A standard arrangement of (100 mg/mL-1 PSES) was ready by dissolving the medication (capsules, syrup and drop) in distilled water. To produce solutions with lower concentrations, the stock solution was appropriately diluted. A fresh 0.2% (w/v) solution was made by dissolving 100 mg of NBD-Cl (Sigma Chemical Co., St. Louis, MO, USA) in 100 mL of methanol. 500 mL of distilled water and 8.8 mL of concentrated sulfuric acid solution were mixed to produce 0.2 mol-1 of hydrochloric acid. In order to create the sodium phosphate-hydroxide solution, 100 milliliters of potassium dihydrogen phosphate (0.1 $mol^{-1}$) and sodium hydroxide (0.1 $mol^{-1}$) were combined until the pH was between (6.0 and 10.5).

**General Procedure**

The top portions of the standard PSES solution, which covered the concentration of PSES in the scope of (0.5-5 mg/mL-1), The items were put into a progression of 10-milliliters volumetric glass flasks. After thoroughly mixing the mixture with 1.0 mL of 0.2% NBD-Cl solution, 0.2 mL of phosphate buffer solution (pH=7.8) was added. After chilling the reaction mixture at 70°C for an hour in a water bath , 2.0 mL of 0.2M HCl arrangement was added to ferment it. After that, the vials were agitated for 20 minutes while being diluted with acetone to the proper level. The amount of fluorescence for the outcome arrangements was evaluated at 532 nm following source of illumination at 475 nm and was contrasted with reagent spaces exposed to indistinguishable treatment. The relative fluorescence intensities were plotted against the final drug concentration to produce a calibration curve. A calibration graph or regression equation that had previously been made was used to measure the amount of PSES.

**Identify the equivalent ratio of the reaction**

The Job's method, which entailed making equimolar aqueous master aqueous solutions (5 * $10^{-4}$ $mol^{-1}$) of PSES and NBD-Cl, was used for continuous contrast. Several solutions were prepared with a fixed total amount of PSES and NBD-Cl. The general procedure that was recommended was then adhered to. The log-linear technique was used: The general methods mentioned above were used to conduct two sets of testing. Various amounts of NBD-Cl (1 * 10-4 to 5 * 10-4mol/L-1) and a decent measure of PSES (1 * 10-5 mol/L-1) were utilized in the principal set of examinations. While, the second series of tests employed different doses of PSES (1 * 10-5 to 2 * 10-6 mol/L-1) and a proper measure of NBD-Cl (5 * 10-4 mol/L-1). The logarithms of the subsequent RFI were plotted against the logarithms of the NBD-Cl and PSES concentrations in the first and second sets of experiments, respectively. The slopes of the fitted lines were calculated for both sets of tests.

**Pharmaceutical Preparation Procedures**

**Analysis of capsules**: The equivalent of 15 capsules, or 20 milligrams, of the complex (PSES) that was manufactured was taken and weighed and was conveyed to a (200 Ml) titration cup with the assistance of a few sections water. After that, water was added to dilute the solution

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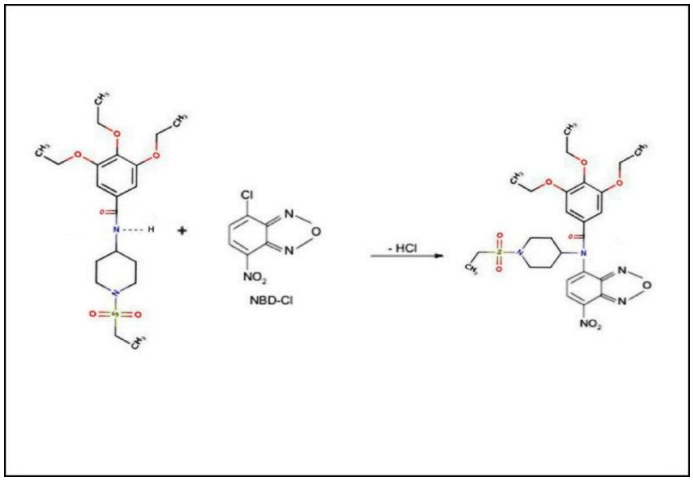
to volume. The residue was repeatedly washed with distilled water and diluted to 100 milliliters after the resulting solution was filtered. To reach a PSES concentration of 100 mg/mL$^{-1}$, parts of the filtrate were quantitatively diluted with distilled water using the basic approach that was suggested. **Droplet and syrup testing**: The syrup and droplet sample was carefully measured to have a volume equal to 20 mg of PSES. It was then transferred to a 200 mL calibration vial and filled with pure water. As required by the experimental conditions, water was added to the resulting solution to modify its concentration, following the basic procedure that was suggested.

## Results and discussion

### Spectra of excitation and emission

Nucleophilic groups like thiols and amines group in the first and second positions have the ability to replace the highly reactive chlorine atom found in NBD-Cl. Although NBD-Cl is not luminous by itself, it produces fluorescent byproducts when it combines with thiols or amines. PSES lacks intrinsic fluorescence, hence in order to identify it using fluorescence spectroscopy, it had to be derivatives using a fluorescent probe. In the present investigation, a bright fluorescent addition product was produced by the reaction of PSES using NBD-Cl while phosphate buffer (PBS) is present (pH = 7.8) (Plot 2). Under the given exploratory circumstances, the fluorescence arrives at its greatest power at excitation and discharge frequencies of 475 and 532 nanometers, separately. The excitation and discharge spectra of the PSES response item with NBD-Cl are displayed in (Figure 1).




**Scheme 2.** Utilizing a phosphate solution with a pH of 7.8, the suggested interaction pathway between PSES and NBD-Cl is demonstrated.

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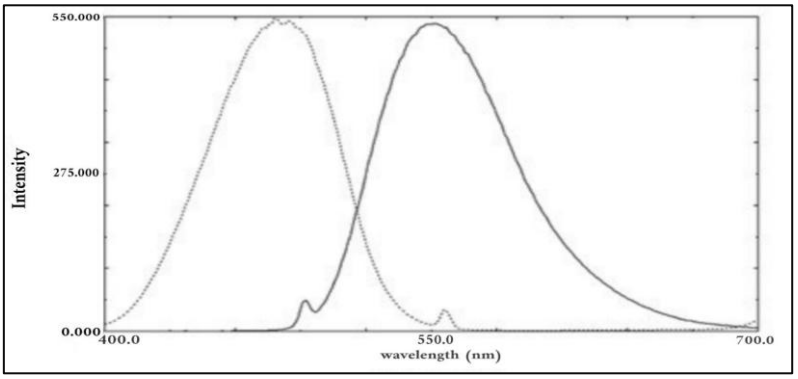


**Figure 1.** The spectra of emission (—) and excitation (...) for the reaction of (5 mg/mL) PSES with NBD-Cl.

**Optimizing the parameters of the investigation**

The several experimental factors (heating duration, temperature, diluent solvent, pH, buffer solution type, hydrochloric acid concentration and NBD-Cl) that influence color development and stability have been thoroughly examined and improved.

**The influence of heating time and temperature.**

At room temperature, the reaction rate was extremely slow, according to preliminary studies. The derivation in this study was carried out throughout a range of time periods and temperatures, from 45-100 °C. After 50 minutes of heating to 75°C, the reaction was finished, as seen in (Figure 2). The reaction could not be finished at the lower temperatures (35-60°C). The fluorescence intensity reached its maximum at higher temperatures (85-100 °C) in shorter periods of time (5 and 15 minutes). However, as interaction duration increased, measurements rapidly and gradually decreased. This might be because high temperatures cause the reagent to degrade [10]. As a result, additional tests were carried out for 60 minutes at 75°C.

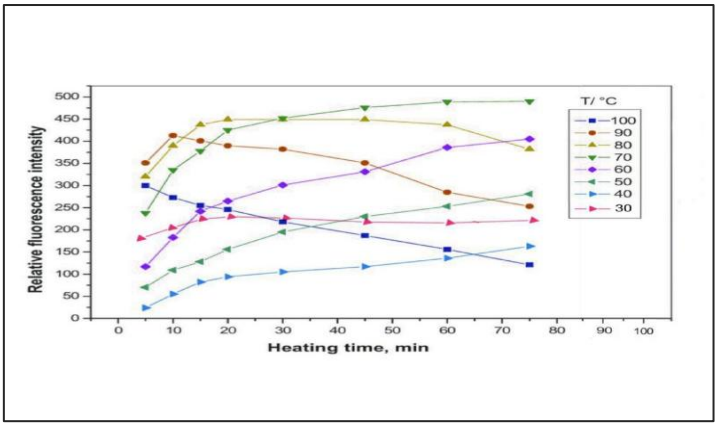


**Figure 2.** The impact of heating time and temperature on PSES's reaction with NBD-Cl.

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**The impact of the diluted solvent, buffer solutions and pH.**

A variety of solvents, including acetone, ethanol, acetonitrile, methanol, isopropyl alcohol, DMF and water, were investigated in order to determine which one would be best for dilution. Because it offers the highest sensitivity, acetone was selected for more research after the experimental findings showed that it was the most appropriate diluent (Figure. 3).

As demonstrated in (Figure 4), the impact of pH on the system's fluorescence intensity was investigated because pH plays a significant role in the reaction. To find the best conditions for calculating PSES, four different types of media were assessed: buffer solutions of (phosphate-NaOH (ph NaOH, borax-NaOH (BO NaOH), citrate-NaOH (CI NaOH), and Tris-HCl (TNaOH)). The P-NaOH buffer system produced the highest fluorescence intensity, presumably as a result of the much slower rate at which NBD-Cl broke down into 2-hydroxy-7-nitrobenzofurazan (NBD-OH). This outcome aligned with the findings of Miyano et al. [11,12]. The pH range of 7.6 to 8.0 was where the increased fluorescence reached its highest intensity. As a result, a pH of 7.8 was selected for more research [13]. The derivation was affected when the buffer volume was changed from (0.1 to 5.0 mL). The fluorescence peaked when (0.2 mL) of ($HNaO_5P^{-3}$) solution was added. As a result, the experiment consumed 0.2 mL of the buffer.

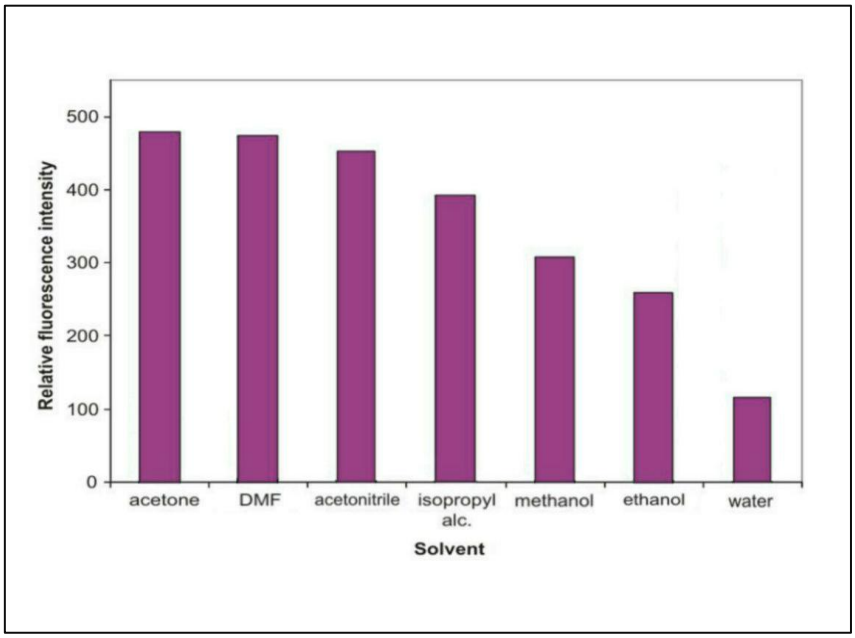


**Figure 3.** The effect of solvents on PSES with concentration (4 mg/mL-1) and NBD-Cl's response.

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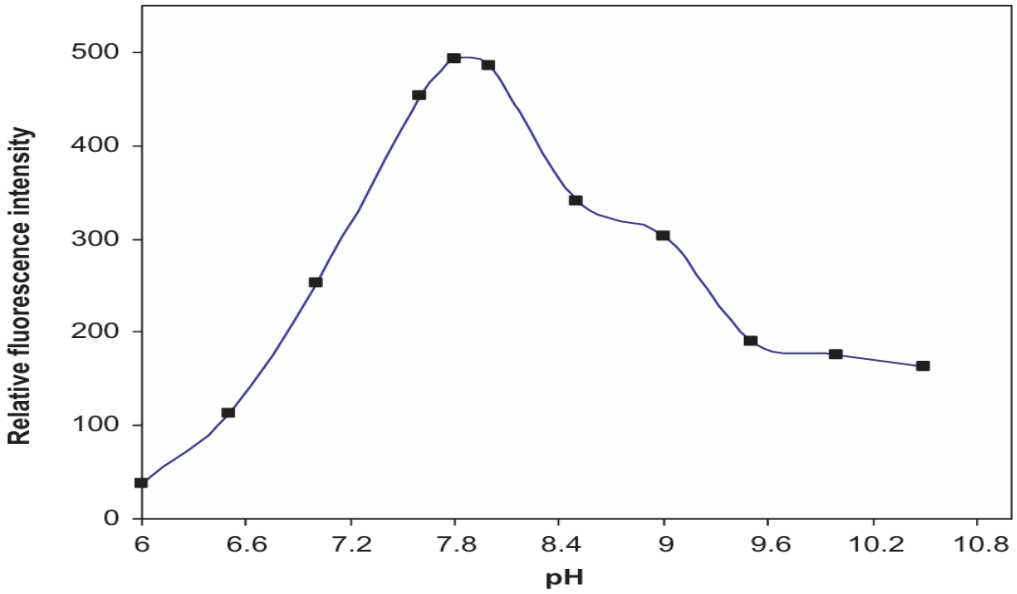


**Figure 4.** The impact of pH on PSES at concentration (4 mg/mL) and NBD-Cl's reacting.

**The Effect of NBD-Cl and HCl concentration**

Assuming all other factors equal, the impact of (0.3% NBD-CL) attentions on the reaction product's fluorescence strength was examined. The 1.0 mL of 0.3% NBD-chloride was employed for the duration of the investigation since it was discovered that increasing the reagent concentration caused the fluorophore's fluorescence intensity to gradually increase more than the 0.9 mL of 0.3% NBD-chloride, after that, it remained steady. (Figure 5). NBD-Cl's hydrolysis product, the prepare compound (NBD-OH), can interfere with the fluorescent product and produce issues [14]. By lowering the working medium's pH to less than 1.0, the hydrolysis product's fluorescence is extinguished [15]. Consequently, the production of (NBD-OH) caused a considerable reduction in background fluorescence when the reaction mixture was acidified prior to fluorescence measurement. Various acids were evaluated to determine which would be best for acidifying the reaction mixture (Figure 6). Because it produced the highest fluorescence intensity, the results showed that hydrochloric acid is the most appropriate acid. A concentration greater than 0.03 mol-1 produced a stable and maximum fluorescence intensity, according to research on the influence of hydrochloric acid concentration. For additional testing, a 2.0 mL volume of 0.2 mol-1 hydrochloric acid was selected.

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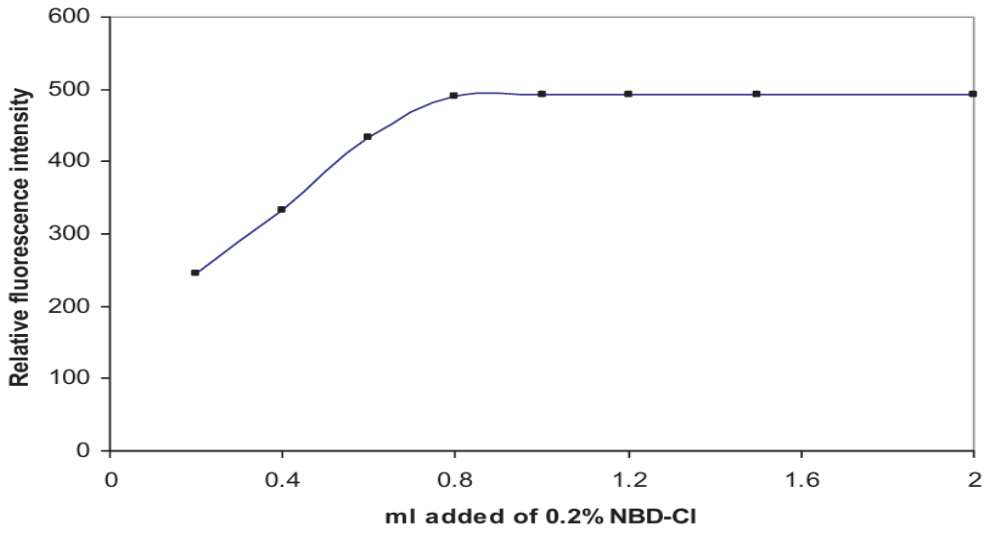


**Figure 5.** The influence of 0.3% NBD-Cl reagent addition on the reaction with PSES at concentration (4 mg/mL-1).

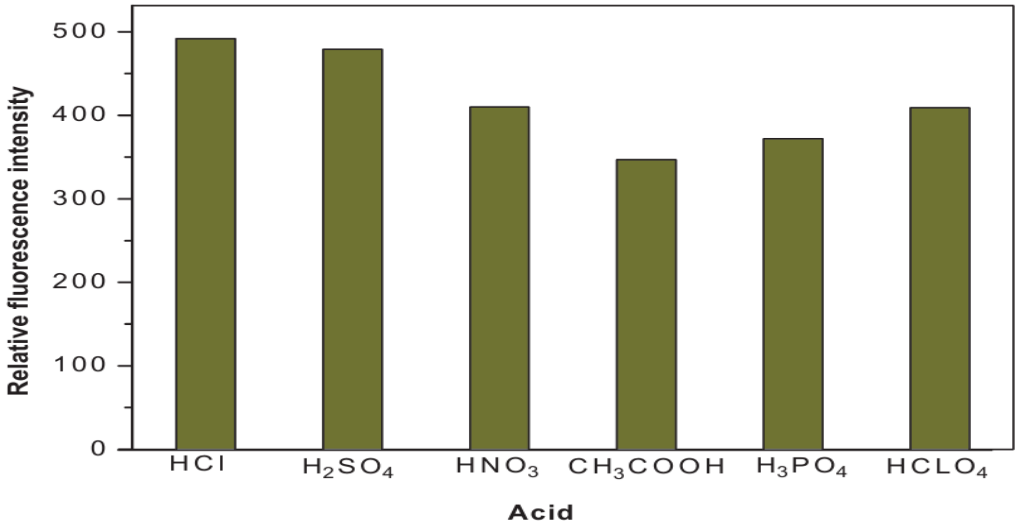


**Figure 6.** The effect of acids on the PSES at concentration (4 mg/mL) reaction with NBD-Cl

### The Effects of Addition Order and Color Development Stability

It was investigated the way the addition order affected the system's fluorescence intensity. The drug (NBD-Cl) buffer addition order produced the best results, according to the outcomes. The product's fluorescence intensity rose over the course of 20 minutes, after that, it remained constant for at least 72 hours at room temperature. Therefore, wholly measurements be there taken twenty minutes later. This improved the technique's usability and allowed it to be used with a large number of samples.

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**The principle of Stoichiometry and the reaction's mechanism**

Under ideal circumstances, (Job's plot) of constant difference and the limiting logarithmic approach were used to examine the stoichiometry of the reaction between PSES and NBD-Cl [16,17]. Job's plot's symmetrical bell shape (Figure. 7) shows the PSES compound and that the (NBD-Cl) as complex percentage was 1:1. Two straight lines were produced using the limiting logarithmic technique (Fig. 8). The slopes of these lines had values of 0.7532 and 0.6738, which validated the reaction's 1:1 ratio. This ratio led to the hypothesis that the chemical route between PSES and NBD-Cl would continue as Scheme 2 illustrates.

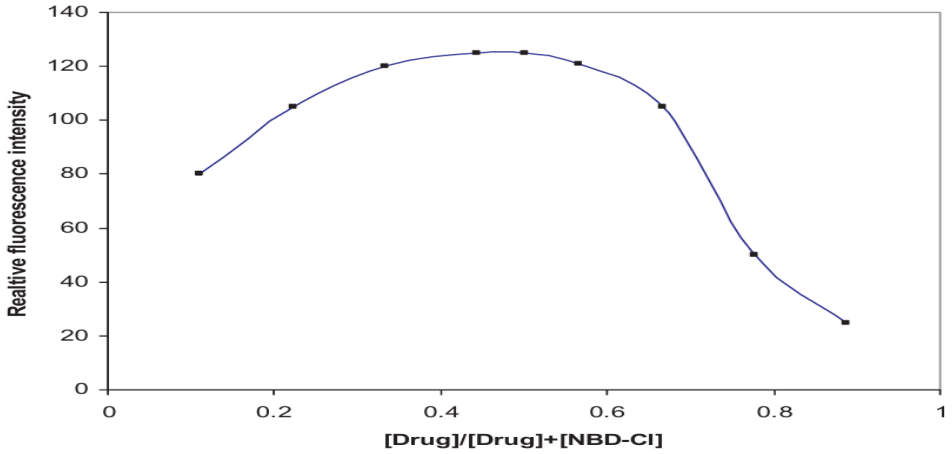


**Figure 7.** Job's Plot is used to assess the stoichiometry of the reaction between PSES and NBD-Cl.

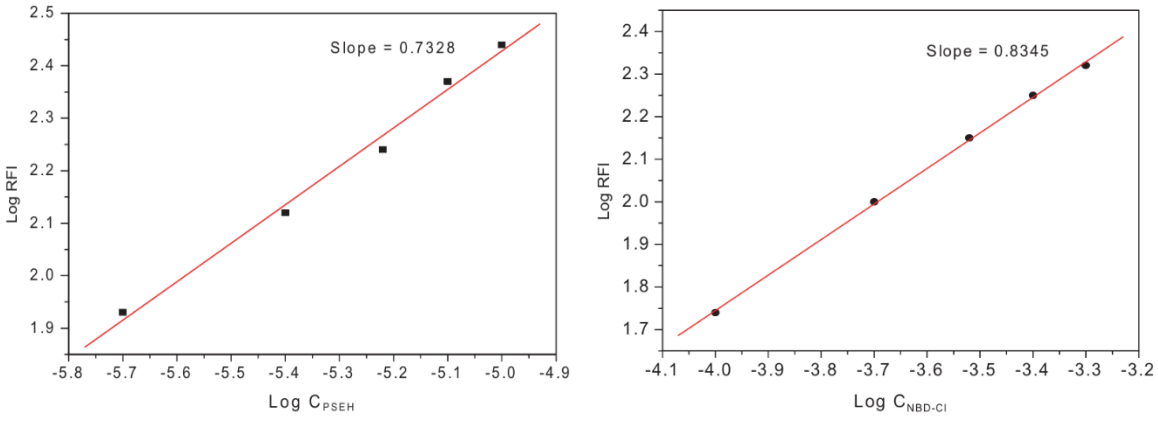


**Figure 8.** The limiting logarithmic plot is used to show the molar reactivity of PSES with NBD-Cl. The first line was constructed using varying NBD-Cl concentrations and fixed PSES concentrations. The second line was made using a fixed NBD-Cl concentration and variable PSES concentrations.

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**Evaluation of the proposed methodology**

**Linearity; (LOQ and LOD)**

The calibration graph was created using the designated ideal reaction conditions. The performance information for the suggested approach is shown in Table 1, which also includes the correlation coefficient, linear range, regression equation, limit of quantitation (LOQ), and limit of detection (LOD). To evaluate linearity, PSES was determined at five unmistakable fixation levels and every focus was broke down multiple times. As per the information in Table 1, there is a direct relationship between's the centralization of PSES from (0.5-5 mg/mL-1) and The force of the fluorescence. With a connection coefficient of 0.97, the functioning focus range showed great linearity. By figuring out the bottom attentiveness that could be stately, LOQ was established [18]. Founding the lowest level at which the analytic may be consistently detected allowed for the determination of LOD (Table 1). The following formula was used to determine LOQ and LOD [10]. LOQ=10σ/s …1, LOD= 3σ/s….2. where S is the calibration curve's slope and σ is the standard deviation of the regression line's intercept.

**Table 1.** The spectrofluorometric measurement of PSES according to its interaction with (NBD-Cl): experimental and analytical data.

| Factors | Assessment |
|---|---|
| Linear range, mg/mL-1 | 0.5-5 |
| Slope | 86.6 |
| Correlation coefficient (r) | 0.97 |
| Solvent | Acetone |
| λ em,nm | 525 |
| λ ex,nm | 480 |
| F = a+bC | - |
| $S_b$ | 1.231 |
| $S_a$ | 0.122 |
| Intercept | 13.25 |
| LOQ, mgmL-1 | 0.3647 |
| LOD, mg/mL-1 | 0.181 |

Accuracy and precision. PSES samples with concentrations of 0.5, 3, and 5 mg/mL-1 for consecutive days were utilized to assess the intraday and intraday accuracy of the proposed spectrofluorometric strategy [19]. The scientific outcomes showed in (Table 2) demonstrated that the RSD for intraday and intraday accuracy were (0.4025-0.8171).Relative error, which ranged from 0.05 to -0.1%, was used to calculate the accuracy of the suggested approach. The assay demonstrated decent accuracy and precision together with outstanding consistency, according to the results.

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**Table 2.** PSES intra-day accuracy and precision with the proposed approach

| Method indicated | C (mg/mL$^{-1}$) | | Recovery, % | Relative standard deviation % | relative error % |
|---|---|---|---|---|---|
| | Taken | SD | | | |
| Interaday | 1 | 0.99±1.72 | 99.97 | 0.5133 | -0.12 |
| | 2 | 1.99 ±1.28 | 99.98 | 0.2876 | -0.01 |
| | 3 | 3.0±1.26 | 100.05 | 0.6608 | -0.05 |
| Intraday | 1 | 0.99±1.41 | 99.96 | 0.8120 | -0.2 |
| | 2 | 1.99 ±1.16 | 99.97 | 0.6012 | -0.1 |
| | 3 | 3.01±2.23 | 99.99 | 0.5121 | -0.05 |

**Table 3.** Utilizing the recommended strategy to measure PSEH in pharmaceutical formulations

| Formulations for drugs | F-test[b] | t-Test[b] | SD[a] | Reported method |
|---|---|---|---|---|
| Decongess SR | 1.475 | 1.6758 | 99.98±1.054 | 97.85±1.330 |
| Triaminic | 1.933 | 0.8338 | 100.23±0.916 | 100.11±0.981 |
| Sudophine | 1.546 | 1.9351 | 100.09±0.7235 | 99.91±0.602 |

[a]Values are mean of five determinations SD.
[b]Theoretical values for t and F at 95% confidence limit (n = 5) were 2.78 and 6.39, respectively.

**Analysis of drugs**

The suggested approach was effectively used to determine the PSES content of commercial drops, syrup, and capsules. As shown by the magnificent recuperation (Table 3), the accuracy and exactness of the information were adequate.The findings of the drug's cover research and formulation analysis (Table 3) indicated that no additives or excipients were interfering with the formulations. Student’s-and-F-tests were used to statistically compare the accuracy and precision of the suggested approach with a documented method at a 95% confidence level. There is no discernible difference in accuracy or precision between the suggested and reported methods because the t- and F-values did not surpass the theoretical values [20,21]. Recovery studies using the conventional addition method were conducted to assess the correctness of the suggested approach. in the PSES assessment. At the amounts found in dose forms, it was found that powder, glucose, wheat, lactose, dextrose, and magnesium stearate didn't influence the estimation. The findings of the pharmaceutical formulation, which are displayed in Table 3, make this clear.

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**Table 4.** PSES in medication formulations can be determined using the standard addition procedure.

| Formulations for drugs | Occupied, $mg/mL^{-1}$ | Additional, $mg/mL^{-1}$ | Originate, $mg/mL^{-1}$ | Retrieval, % |
|---|---|---|---|---|
| Capsules(120 mg) PSES | 0.5 | 1 | 1.574 | 99.77 |
| | | 2 | 1.998 | 100.43 |
| | | 3 | 2.945 | 101.27 |
| Syrup(5 ml,10 mg) PSES | 1.0 | 0.5 | 1.615 | 100.58 |
| | | 1 | 2.108 | 99.24 |
| | | 1.5 | 2.613 | 101.01 |
| Drops (0.7 ml,7.5 mg) PSES | 1.5 | 0.5 | 2.012 | 99.66 |
| | | 1.5 | 3.011 | 99.45 |
| | | 2.5 | 4.102 | 99.37 |

## Conclusion

The newly created spectrofluorometric approach for determining PSES is specific, dependable, sensitive, and cost-effective, it can be concluded. The suggested technique has good accuracy and precision when measuring concentrations as low as 0.5 $mg/mL^{-1}$. Additionally, it was effectively used to determine the dosage and pure form of pseudoephedrine Sulfate. To identify a sympathomimetic medication, pseudoephedrine hydrochloride, a novel, profoundly touchy, and explicit spectrofluorometric procedure has been concocted. The current technique produced a highly luminous product that was measured at 532 nm (excitation at 475 nm) by derivatization with 2-Chloro-7-Nitrobenzo -2-Oxa-1, 3-Diazole in phosphate buffer at pH 7.8. The fluorescence intensity and pseudoephedrine hydrochloride concentration were shown to have a linear relationship and strong correlation at optimal conditions, ranging from 0.5 to 5 $mg/mL^{-1}$. The suggested approach was effectively used to test for pseudoephedrine hydrochloride in commercial pharmaceutical formulations with high precision and accuracy, free from common additive interference. A statistical analysis of the data using a recognized methodology revealed good agreement and demonstrated that the accuracy and precision did not differ significantly. The reaction's stoichiometry was established, and the reaction route was hypothesized.

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