Spectrophotometric Assay of Salbutamol Sulfate in Pharmaceutical Forms by Chlorination Reaction

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A simple, inexpensive, environmentally friendly, sensitive, and selective spectrophotometric method was developed for the determination of salbutamol sulfate (SAL) in its pure form and in pharmaceutical preparations. The method is based on the chlorination reaction of salbutamol sulfate using sodium hypochlorite to form a chloro-derivative of SAL and the excess (unreacted) sodium hypochlorite was subsequently removed by treatment with nitrite ion. The color development occurs through the oxidation of iodide by the chloro-derivative of SAL to iodine in the presence of starch, which leads to form a blue colored product, and its absorbance was measured at 568 nm. Under the optimized reaction condition, a linear relationship was obtained over the concentration range of 1-17 μg mL^{-1} and obeyed Beer's law with a determination coefficient (R^2) = 0. 9992. The molar absorptivity and Sandell's sensitivity were found to be 2.81×10^4 L mol^{-1} cm^{-1} and 2.05 ×10^{-2} μg cm^{-2}, respectively. The limit of detection (LOD) and limit of quantification (LOQ) were 0.113 μg mL^{-1} and 0.379 μg mL^{-1}, respectively. The proposed method was successfully applied for the determination of SAL in pure form and in various pharmaceutical preparations, including tablets, syrups, and inhalation solution, yielding satisfactory recovery percentages ranging from 98.9% to 100.4% and without interference from common excipients, thus confirming the possibility of adopting this method in routine analytical laboratories.

Keywords: salbutamol sulfate (SAL), sodium hypochlorite, starch, chlorination reaction, spectrophotometry

Introduction

Salbutamol sulfate ($C_{26}H_{44}N_2O_{10}S$) is chemically known as Bis[4-[(1RS)-2-(tert-butyl amino)-1-hydroxy-ethyl]-2-(hydroxymethyl)phenol] sulfate with molecular weight 576.7 g.mol^{-1} and its white and freely soluble in water with chemical structure explain in Fig. 1 [1].

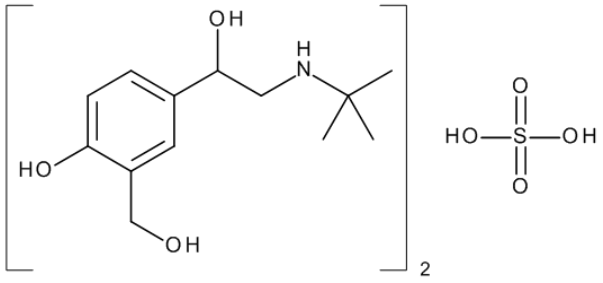

Fig. 1. Chemical structure of salbutamol sulfate.

Salbutamol is one of the selective short-acting β_2-adrenergic receptor agonists (SABAs) introduced as a rapid-relief medication for the management of asthma symptoms, and its therapeutic action is primarily attributed to its strong broncho dilatory effect, which results from selective stimulation of β_2-adrenergic receptors located in bronchial smooth muscle [2]. For decades, Salbutamol has been used to alleviate bronchospasm in airway disease [3].

Salbutamol is administered via an inhaler to patients experiencing exacerbations of asthma or chronic obstructive pulmonary disease (COPD), also it is used to arrest preterm labor [4, 5].

Given the significant therapeutic importance of salbutamol sulfate, it has received considerable attention in pharmaceutical analysis for its determination as a pure form and in its various pharmaceutical preparations. Numerous analytical methods have been developed for this purpose, including chromatographic methods such as using achiral supercritical fluid chromatography [6], high performance liquid chromatography(HPLC) [7], also and RP-HPLC method using modified clay-activated carbon adsorbents [8], and there are also hyphenated technique such as LC-MS/MS [9] and UPLC-MS/MS [10], and by electroanalytical voltammetry [11, 12], also by using green potentiometric electrode [13], Flow injection analysis [14,15]. Most of the analytical methods and techniques mentioned require expensive equipment and skilled operators and are often unavailable in routine analytical laboratories. Therefore, several spectroscopic methods for the determination of salbutamol sulfate have been proposed as suitable analytical alternatives including diazotization coupling reactions and formed azo dye [16–18], oxidative coupling reactions [19–21], dye-bleaching reactions [22, 23].

In this study, a simple and sensitive spectrophotometric method was proposed for the determination of salbutamol sulfate, which involves the reaction of salbutamol sulfate with sodium hypochlorite, followed by removal of the excess sodium hypochlorite using sodium nitrite.

The chlorinated salbutamol sulfate then acts as oxidizing agent and converting iodide to free iodine. The liberated iodine reacts with starch to form a blue-colored complex whose absorbance intensity is directly proportional to the concentration of salbutamol sulfate. Therefore, the proposed method can be considered accurate, sensitive, and cost effective, as it does not require expensive instruments or sophisticated reagents and chemicals that may not be readily available in routine analytical laboratories.

Experimental part

Instruments

All spectrophotometric measurements and spectral scanning were performed using a SHIMADZU UV-Vis 1900i spectrophotometer with glass cells having a light path length of 1 cm. A Kern & Sohn GmbH ABS 120-4 electronic balance was used to weigh solid materials.

Materials and reagents

The chemical materials used in this study were of high purity and were used as received without any additional purification.

Preparation of solutions

Salbutamol sulfate standard solution (100 μg mL^{-1}). A 0.0100 g of pure salbutamol sulfate was dissolved in distilled water and then diluted it to 100 mL in a volumetric flask.

Reagent solution KI-Starch was prepared by weight 0.750 g of soluble starch and dissolved in 100 mL boiling water and after 5 min 1.00 g of potassium iodide was added to solution and then boiling this solution for an additional 5 min.

The solution remained colorless for several days when protected from light and stored at 10 °C when not in use [24].

Sodium hypochlorite solution (1×10^{-2}M). A 1.250 mL portion of NaOCl was diluted with distilled water in 100 mL volumetric flask.

Sodium nitrite solution (6% m/v). A 6.00 g of sodium nitrite was dissolved in distilled water and diluted it to 100 mL in a volumetric flask.

Preparation the pharmaceutical solution

Nutadeen syrup (100 μg mL^{-1}). A 12.5 mL portion of Nutadeen bronchodilator syrup (each 5 mL contains salbutamol as sulphate) (Aswar Al-Khaleej Co., Samarra, Iraq) was transferred into a 50 mL volumetric flask and diluted with distilled water.

Tablets (100 μg mL^{-1}). Ten tablets of Butadin (Samarra, Iraq) (each tablet contains 2 mg of salbutamol as sulphate) were ground, dissolved in distilled water, filtered through filter paper, and then diluted to 100 mL in a volumetric flask.

Salpium inhalation solution (100 μg mL^{-1}). A 5 mL portion of inhalation solution (Bilim Co., Türkiye) (each single-dose vial contains 2.5 mL of solution equivalent to 3.01 mg salbutamol sulfate) was transferred into a 50 mL volumetric flask and diluted with distilled water.

Principle of method

The method involves the indirect determination of salbutamol sulfate by the formation of a triiodide–starch complex responsible for the blue color. The reaction involves three steps. The first step is the chlorination reaction of the secondary amino group of SAL by sodium hypochlorite (SHC) to form chlorinated SAL. The second step involves reducing the unreacted sodium hypochlorite with sodium nitrite. The third step involves the oxidation of iodide to iodine by chlorinated SAL, and the blue color is produced due to the formation of the triiodide–starch complex (Fig. 2).

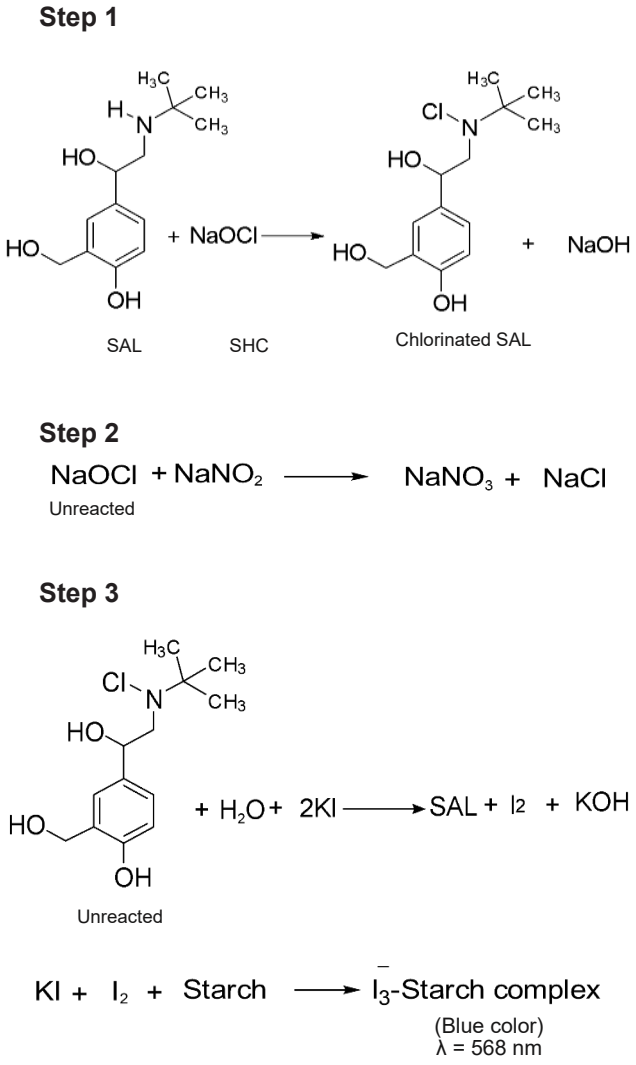

Fig. 2. The proposed equations for the three steps of reaction.

Results and Discussion

Optimum conditions

Effect of the presence of acid or base. Upon the addition of 1 mL of acid (1 M HCl), no color change was

observed. Similarly, the addition of 1 mL of 1 M NaOH did not improve the color development. Therefore, the addition of acid or base was not recommended.

Effect of the type of oxidizing agent. To determine the effect of the type of oxidizing agent on the absorbance intensity of the formed product at 10 μg/mL, 1.0 mL of each of the following 1×10^{-2} M oxidizing agents, NaOCl and $Ca(OCl)_2$, was examined. Sodium hypochlorite gave slightly higher absorbance and demonstrated better color stability (Fig. 3). Therefore, it was adopted in subsequent experiments.

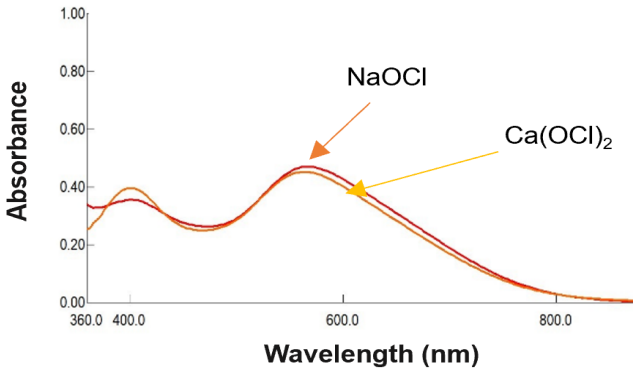

Fig. 3. Absorption spectra of oxidizing agents.

Effect of sodium hypochlorite volume. To determine the optimum volume of sodium hypochlorite required to complete the reaction, increasing volumes (0.5–2.5 mL) of sodium hypochlorite were added to three separate series of volumetric flasks. The first series contained salbutamol sulfate at a concentration of 5 μg mL^{-1}, while the second series contained 10 μg mL^{-1} of salbutamol sulfate, and the third series contained 12.5 μg mL^{-1}, with the other steps of the procedure completed. The addition of 1.0 mL of sodium hypochlorite resulted in the maximum absorbance value for the three concentrations, 5, 10, and 12.5 μg mL^{-1}, indicating completion of the chlorination reaction. Accordingly, this volume was selected as the optimum and was employed in all subsequent experiments.

Effect of chlorination reaction time. After the addition of 1 mL of 1×10^{-2} M sodium hypochlorite to a series of 10 mL volumetric flasks containing 10 μg mL^{-1} of salbutamol sulfate solution, the mixtures were allowed to stand for different periods (0–10 minutes), and the remaining steps of the procedure were then completed. The obtained results indicated that 7 minutes was the optimum chlorination reaction time, as it produced the highest absorbance value

Effect of sodium nitrite volume and time. This study was carried out by adding increasing volumes (0.25–2.0 mL) of 6% sodium nitrite solution to a series of 10 mL volumetric flasks containing 10 μg mL^{-1} of salbutamol sulfate solution, a volume of 0.5 mL of 6% sodium nitrite solution was found to be optimal, as it gave the highest absorbance value. Therefore, this volume was selected for the subsequent reaction's procedure. Sodium nitrite solution was added to a series of 10 mL volumetric flasks containing 10 μg mL^{-1} of salbutamol sulfate solution and 1 mL of sodium hypochlorite, and waiting for different time intervals (0-15 minutes), 5 minutes was selected due it gave the optimum absorbance value.

Effect of KI-Starch reagent volume. In order to establish the optimum reagent volume necessary for completing reaction and gave maximum absorption, increasing volumes (0.5-2 mL) of the prepared reagent were introduced into a series of 10 mL volumetric flasks containing 10 μg mL^{-1} of salbutamol sulfate and remaining other optimized reaction components. A reagent volume of 1 mL yielded the maximum absorbance intensity and was selected and fixed for subsequent experiments.

Effect of time before dilution with distilled water. All reaction components were transferred into a series of volumetric flasks, each containing 10 μg mL^{-1} of salbutamol sulfate solution and under the previously optimized reaction conditions, after completion of the reaction and development of the color and before dilution with distilled water were waiting for different time intervals (0-7 minutes) and then diluted by distilled water. The results of this study indicated that two minutes is optimal.

Effect of using solvents. To investigate the effect of using organic solvent instead of distilled water as dilution media. All reaction components were added according to the previously optimized condition into a series of volumetric flasks each of them containing 10 μg mL^{-1} of salbutamol sulfate solution and then were diluted separately with ethanol, methanol, acetone and acetic acid. The results showed that upon dilution with ethanol, methanol and acetone, the reaction mixture became turbid with disappearance of the developed color and when dilution with acetic acid produced a highly turbid solution with a very dark (almost black) coloration. Therefore, organic solvents were excluded, and selected the distilled water was selected as the optimal dilution medium.

Effect of surfactants. A series of 10 mL volumetric flasks was prepared with each one containing 10 μg mL^{-1} of salbutamol sulfate solution with all reaction components under the previously optimized conditions. After completion of the reaction and development of the blue color 1 mL of (CTAP 1×10^{-3} M, Triton 1% M, CPC 1×10^{-3} M, SDS 1×10^{-3} M) was added separately to each flask. The results indicated that the addition of surfactants did not produce any significant enhancement in absorbance values. so, the use of surfactants was excluded from the proposed method.

Effect the time on the stability of the final product. The effect of time on the stability of the final product colored was investigated by measuring the absorbance of two different concentrations 5 and 10 μg mL^{-1} under predetermined reaction condition, and the absorbance was measured every 5 or 10

minutes, and the obtained results indicated that the formed color final produce was stable for 30 minutes.

Final absorption spectrum. After establishing the optimal reaction conditions, the absorption spectrum of a 10 μg mL^{-1} salbutamol sulfate solution was recorded. The maximum absorbance was observed at 568 nm (Fig. 4).

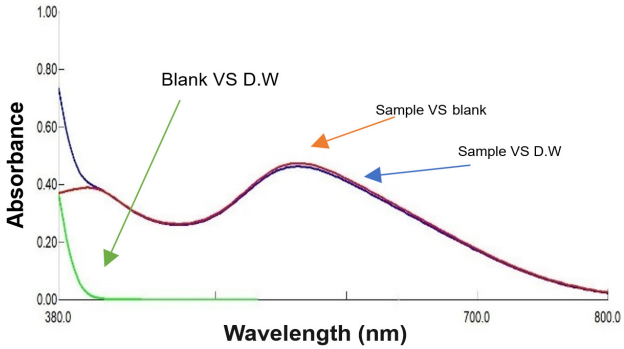

Fig. 4. Absorption spectrum of the final reaction product.

Calibration curve. Under the previously optimized reaction conditions, 1mL of 1×10^{-2} M sodium hypochlorite solution, 0.5 mL of 6% sodium nitrite solution, and 1 mL of prepared reagent KI-Starch were added to a series of 10 mL volumetric flasks containing increasing concentrations (1-17 μg mL^{-1}) of salbutamol sulfate standard solution (100 μg mL^{-1}). After 2 min, the solutions were then dilution to the mark with distilled water, and then the absorbance was measured at 568 nm against a blank solution. A linear calibration curve was obtained over the studied concentration rang, and obeying Beer's law with determination coefficient R^2 = 0.9992 and the molar absorptivity and Sandell's sensitivity were 2.81×10^4 L mol^{-1} cm^{-1} and 2.05 ×10^{-2} μg cm^{-2}.

The limit of detection (LOD) and limit of quantification (LOQ) were calculated for 10 replicates of 1 μg/mL (C_{low}) by using the below equations: LOD = 3σ/s, LOQ = 10σ/s, where σ is the standard deviation of the replicate measurements and s is the slope of the calibration curve. The results obtained were 0.11 μg mL^{-1} and 0.36 μg mL^{-1}, respectively. The main analytical parameters of the proposed method are summarized in Table 1.

Accuracy and precision of method. The accuracy and precision of the proposed method were evaluated by measuring the absorbance at two different concentrations (5 and 10 μg mL^{-1}), and each concentration was analyzed in five replicates. The obtained results indicated that the proposed method exhibited good accuracy and precision, as demonstrated by the calculated values of relative standard deviation (RSD%), relative error (RE%), and recovery (%). The RSD values did not exceed 0.768%, the RE values ranged from −1.4 to 0.4%, and the recovery values ranged from 98.8 to 100.4%.

Table 1. Analytical parameters of the proposed method.

Parameter	Value
Linearity rang (μg mL^{-1})	1-17
Molar absorptivity (L mol^{-1} cm^{-1})	2.81×10^4
Sandell's sensitivity (μg cm^{-2})	0.0205
Limit of detection, LOD (μg.mL^{-1})	0.11
Limit of quantification, LOQ (μg mL^{-1})	0.36
Recovery (%) of 10μg mL^{-1}	100.4
Relative standard deviation, RSD (%)	0.302
Determination coefficient (R^2)	0.9992

Application

The proposed spectrophotometric method was successfully applied to the determination of salbutamol sulfate in various pharmaceutical preparations, including syrup, tablets, and inhalation solution. Sample solutions equivalent to 100 μg mL^{-1} of salbutamol sulfate were prepared from the pharmaceutical formulations. The results obtained at two concentration levels are summarized in Table 2. Good agreement was observed between the found and nominal values, indicating satisfactory accuracy and reliability of the proposed method. These results confirm the suitability of the method for the quantitative determination of salbutamol sulfate in different pharmaceutical dosage forms.

Standard addition method

To assess the accuracy of the proposed method and evaluate possible matrix effects, the standard addition method was applied to the pharmaceutical preparations. Known amounts of standard salbutamol sulfate were added to samples of the syrup, tablets, and inhalation solution, and the resulting solutions were analyzed under the optimized experimental conditions.

The results are presented in Table 3. Recoveries ranged from 97.80 to 102.00%, with relative errors ranging from −2.20 to +2.00%, indicating satisfactory accuracy and negligible interference from the pharmaceutical matrices. These results demonstrate that the proposed spectrophotometric method is suitable for the quantitative determination of salbutamol sulfate in different pharmaceutical dosage forms.

Comparison of the proposed method with reported methods

The analytical performance of the proposed spectrophotometric method was compared with that of previously reported methods for the determination of

Table 2. Application of the proposed spectrophotometric method for the determination of salbutamol sulfate in pharmaceutical preparations.

Pharmaceutical preparation	Amount µg/100 mL Taken	Found	Recovery * (%)	RE* (%)	RSD* (%)	t_{exp} (N=5)	Drug content (mg)
Sample A – Nutadeen syrup, 2 mg/5 mL, Aswar Al-Khaleej Co., Samarra, Iraq	5	4.96	99.20	-0.80	1.99	t_{exp} = 0.90	1.984
	10	10.07	100.70	0.70	0.76	t_{exp} = 2.06	2.014
Sample B – Butadin tablets, 2 mg, Samarra, Iraq	5	5.03	100.60	0.60	2.54	t_{exp} = 0.53	2.012
	10	9.99	99.90	-0.10	1.28	t_{exp} = 0.17	1.998
Sample C – Salpium inhalation solution, 3.01 mg/2.5 mL, Bilim Co., Türkiye	5	5.07	101.40	1.40	2.14	t_{exp}= 1.46	3.052
	10	9.97	99.70	-0.30	0.58	t_{exp}= 1.16	3.001

* average of five determinations. t_{exp} value was calculated using the formula: $t_{exp} \pm = \sqrt{N}/s \cdot (\overline{X}-\mu)$.

Table 3. Results of the standard addition method for the determination of salbutamol sulfate in pharmaceutical preparations using the proposed spectrophotometric method.

Pharmaceutical preparation	Amount µg/100 mL Added	Found	Recovery (%)	RE (%)
Sample A – Nutadeen syrup, 2 mg/5 mL, Aswar Al-Khaleej Co., Samarra, Iraq	5	4.95	99.00	-1.00
	8	8.10	101.25	1.25
Sample B – Butadin tablets, 2 mg, Samarra, Iraq	5	5.04	100.80	0.80
	8	7.93	99.12	-0.88
Sample C – Salpium inhalation solution, 3.01 mg/2.5 mL, Bilim Co., Türkiye	5	4.89	97.80	-2.20
	8	8.16	102.00	2.00

salbutamol sulfate. The comparison was based on key analytical parameters, including the linearity range, molar absorptivity, sensitivity, limit of detection (LOD), limit of quantification (LOQ), accuracy, and precision. The results summarized in Table 4 indicate that the proposed method provides satisfactory analytical performance that is comparable to that of previously reported methods.

The proposed method exhibits a suitable linear dynamic range and high molar absorptivity, together with satisfactory LOD and LOQ values. In addition, the obtained accuracy and precision were within acceptable analytical limits, supporting the reliability of the method for routine analysis. Furthermore, the proposed procedure is simple and cost-effective and does not require sophisticated instrumentation. These characteristics make it a practical alternative for the quantitative determination of salbutamol sulfate in pure form and pharmaceutical preparations.

Greenness assessment

Green analytical chemistry has become an essential part of modern analytical chemistry, aiming to develop environmentally friendly and highly efficient analytical methods. Its primary goal is to reduce environmentally impact by minimizing the use of hazardous chemicals and energy consumption to decrease the generation of harmful waste, while maintaining high and reliable analytical performance suitable for routine analysis. This approach has gained particular importance in the field of pharmaceutical analysis [25].

There are many assessment tools for evaluating the environmental impact of analytical methods, one of these tools is the green analytical procedure index (GAPI). This index encompasses the entire analytical procedure, including sample preparation, reagents and solvents used, energy consumption, and the amount of waste generated. The GAPI index is represented by a five-part diagram, each part of which represents a section of the analytical procedure and these parts are colored red, yellow or green, with each color indicating the level of environmental impact (high, medium, or low, respectively). A high percentage of green parts indicates a more environmentally friendly method. The importance of

Table 4. Comparison of the analytical performance of the proposed method with a reported spectrophotometric method for the determination of salbutamol sulfate.

Analytical parameter	Present method	Literature method [20]
Type of reaction	**Chlorination reaction**	**Oxidative coupling reaction**
Reagent used	KI-Starch	*p-Amino-N,N-diethylaniline sulfate*
Beer's law range μg mL^{-1}	1-17	15-55
λ_{max} (nm)	568	651
Molar absorptivity (L mol^{-1} cm^{-1})	2.81×10^4	0.85×10^4
RSD (%)	≤0.768	0.392–1.567
Sandell's sensitivity (μg cm^{-2})	0.0205	0.0641
Coefficient of determination (R^2)	0.9992	0.9956
Recovery (%)	99.20–101.40	102.181 (mean)
Application	Tablets, syrup and inhalation solution	Tablets and syrup

this assessment lies in comparing different analytical methods to select the most sustainable ones [26, 27]. Compared to conventional techniques such as high-performance liquid chromatography HPLC [28], as illustrated in the Fig. 5, the proposed spectroscopic method exhibits a lower environmental impact due to the absence of organic solvents, relying instead on water, and the elimination of toxic organic reagents, less waste, along with reduced energy consumption compared to HPLC. Give the increasing preference for environmentally friendly methods in quality control and routine analysis within pharmaceutical laboratories, the proposed method can be adopted for the determination of salbutamol sulfate in its pure form and in pharmaceutical preparations.

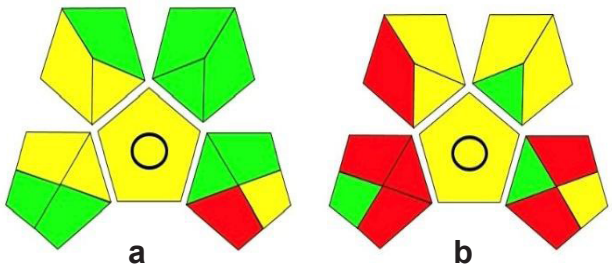

Fig. 5. Comparison of the GAPI pictograms for the proposed spectrophotometric method (a) and the reported HPLC method [28] (b).

To enhance the environmental assessment and provide an accurate quantitative measurement that proves the sustainability of the proposed method, AGREE (analytical Greenness) program was used, which is based on the twelve principles of green analytical chemistry. This program is characterized by providing a numerical (Score) ranging from 0 to 1 represented by a colored pie chart (pictogram) [29].

The results shown in Fig. 6 indicate that the proposed method for determining salbutamol obtained (0.73), while the conventional HPLC method obtained (0.46), confirming that the proposed method is a sustainable and environmentally friendly option compared to conventional method.

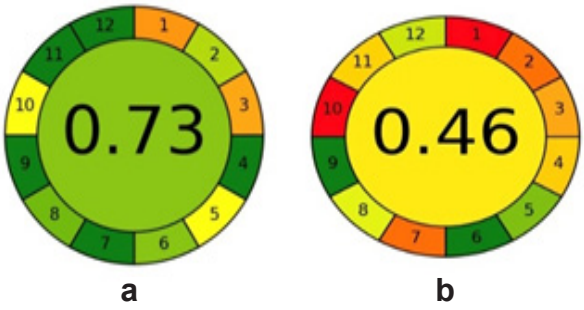

Fig. 6. Comparison of the AGREE greenness scores for the proposed spectrophotometric method (a) and the reported HPLC method [28] (b).

Conclusion

In this study, a new, simple, sensitive, and environmentally friendly spectrophotometric method was successfully developed for the determination of salbutamol sulfate based on its reaction with sodium hypochlorite. The proposed method demonstrated satisfactory accuracy and precision. When applied to pharmaceutical preparations, recovery values ranged from 99.20 to 101.40%, with RSD values ranging from 0.58 to 2.54%. In addition, the standard addition study provided recoveries of 97.80–102.00%, indicating satisfactory accuracy and negligible matrix interference. These results confirm the reliability and applicability of the proposed method for the determination of salbutamol sulfate in both pure form and pharmaceutical preparations.

The proposed method does not require sophisticated or expensive instrumentation, costly reagents, or complex analytical procedures, which enhances its economic feasibility and ease of application. Therefore, it may be considered a practical

and effective analytical approach for the routine determination and quality control of salbutamol sulfate in pharmaceutical laboratories..

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Author's statement

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Authors' contributions

All the authors collaborated in completing this work, as they participated in carrying out the experimental work, data analysis, and preparing the final version of the manuscript.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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