



Utilization of Cloud Point Extraction in Spectrophotometric Determination of Terbutaline Sulfate Using Diazotization and Coupling Reaction

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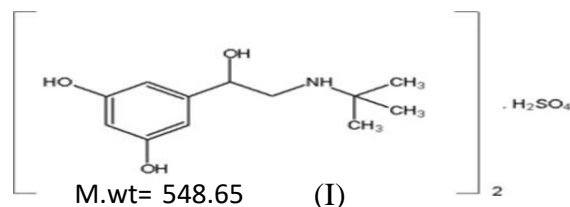
ABSTRACT

A simple, accurate, and efficient cloud point spectrophotometric method, characterized by compatibility and sensitivity, has been described for the estimation of terbutaline sulfate (TbS) in its pure and pharmaceutical formulation as syrup. The procedure was dependent on the reaction of TbS and diazotized 2,4-dinitroaniline (2,4-DNA) in a basic medium, resulting in the formation of an orange azo dye product, which was extracted into Triton x-114 micelles and measured at 448 nm. The conditions of phase separation were studied and optimized. Beer's law was obeyed at concentration ranges of 0.1–13 µg/ml with a molar absorptivity of 1.6×10^6 L. mol⁻¹. cm⁻¹. The limit of detection (LOD) and limit of quantitation (LOQ) were determined and found to be 0.04 and 1.14 µg/ml, respectively, and the average recovery % is 98.91%. The relative standard deviation (RSD) was calculated and found $\leq 1.6\%$. It was also found, through studying the nature of the product, that the azo dye product is formed in a 1:1 ratio of TbS to 2,4-DNA. The method was applied successfully for the determination of TbS in syrup and was free from interference by excipients. The reaction mechanism has been suggested.

Keywords: Spectrophotometry, cloud point, 2,4-dinitroaniline, terbutaline sulfate.

INTRODUCTION

Terbutaline sulfate [2-(*tert*-butylamino)-1-hydroxyethyl] benzene-1,3-diol; sulfuric acid (I) (British Pharmacopoeia, 2013). It is broadly utilized as successful bronchodilator in the management of asthma. Typically utilized as a prophylactic medication as well as to avoid intense exacerbations of asthma, persistent bronchitis, emphysema and other lung illnesses. It unwinds muscles and opens discussion entry within the lungs, making them simpler to breathe (Chanda *et al.*, 2009; Senthilraja and Giriraj, 2011).



TbS has been analyzed using several analytical techniques such as, chromatography (Mai *et al.*, 2020; Rani *et al.*, 2022; Itagimatha *et al.*, 2019; Herring *et al.*, 2000), chemiluminescence (Han *et al.*, 2012; Dong *et al.*, 2018), electrochemical (Toan *et al.*, 2022; Kong *et al.*, 2023; Sun *et al.*, 2022) and fluorometric methods (Omar *et al.*, 2018; Nour-Eldeen *et al.*, 2022; El Abass *et al.*, 2019). Different spectrophotometric methods were described for estimating TbS using various reagents such as Fe (III) in the presence of 1,10-phenanthroline or 2,2'-bipyridyl (Al-Hammoodi *et al.*, 2023), 9-chloroacridine (Jabar *et al.*, 2022) p-chloranilic acid (Hasan *et al.*, 2014), Folin-Ciocalteu (Omar *et al.*, 2018), p-phenylenediamine (Al Majidi *et al.*, 2019), and cerium (IV) (Omar *et al.*, 2018). However; Cloud Point Extraction (CPE) technique is used as an alternative to liquid-liquid extraction, depending on the preconcentration of material in the aqueous medium. Nonionic surfactants form micelles in an aqueous solution, and the solution becomes cloudy when heated to certain temperatures. Surfactants in the above technique are known to have the ability to concentrate these materials (Bezerra *et al.*, 2005; Kori, 2021). So, the aim of this research is to develop CPE spectrophotometric determination of TbS in its pure and pharmaceutical forms. The present method is depended on extracting of azo-dye product, which is produced by coupling TbS with diazotized 2,4-DNA, by Triton x-114.

EXPERIMENTAL

Instruments

Shimadzu UV-1800 PC UV-Visible double-spectrophotometer using quartz cells with a thickness of 1 cm was used for absorption spectra. KERN ABS-Germany sensitive balance was used for weighing the substances. Ultrasonic Shaker Cleaner Power Sonic 405 equipped from Lab Tech-Korea was used for the solvation operations. Water bath type BS-11 from Lab Companion-Korea was used for heating process and pH-meter with a combined glass electrode type Philips PW (9421) was used for pH measurements.

Chemicals and reagents

All chemicals and reagents of high purity used were supplied by Fluka and BDH companies and the drugs used were supplied by SDI.

Terbutaline sulphate (TbS): Prepare a stock solution of 100 µg/ml TbS by dissolving 0.0100 g in 5 ml of distilled water, makeup to 100 ml using the same solvent in a volumetric flask, and place on an ultrasonic shaker for 10 min. to complete dissolution. Then the solution was stored in the refrigerator and was stable for 1 week.

2,4-Dinitroaniline solution (2,4-DNA): This solution was prepared in a concentration of 5.0×10^{-3} mole/L by dissolving 0.0916g of 2,4-DNA in 50 ml acetonitrile with stirring and then diluted to 100 ml in a volumetric flask with distilled water (Saleem *et al.*, 2013).

Hydrochloric acid (HCl): Appropriate volume of conc. HCl was diluted by distilled water to prepare a concentration of $\sim 2.5\text{M}$ in a 100 ml volumetric flask.

Sodium nitrate (NaNO_2): The solution was prepared in concentration of 1% by dissolving 1g of NaNO_2 in 100 ml distilled water.

Sulphamic acid: This solution was prepared in concentration of 3% by dissolving 3g in 100 ml distilled water.

Potassium hydroxide (KOH): This solution was prepared in concentration of 1M by dissolving 5.6g of KOH in 100 ml distilled water.

Triton x-114: This solution was prepared in concentration of 5% by diluting 5ml in 100 ml distilled water.

Procedure for preparing diazotized 2,4-dna

To achieve the optimum conditions for preparing the diazonium salt of 2,4-DNA in the presence of TbS as a coupling agent were studied and the following procedure was given high sensitivity and recommended:

Into a 10 ml volumetric flask, 1ml of 2,4-DNA ($5 \times 10^{-3} \text{ M}$), 0.3ml of HCl (2.5M), and 0.3 ml of sodium nitrite (1%) were added. Shaking for 5 min and followed with addition of 1ml of sulphamic acid (3%) and waiting for 7 min with shaking the solution (Shlear *et al.*, 2020; Rahawi *et al.*, 2011).

General assay procedure for pure drug

Into 10 ml volumetric flasks, the amounts of reagents used in optimum conditions for preparation of diazotized 2,4-DNA were added, followed by the addition of 0.1-13 $\mu\text{g/ml}$ TbS and 1ml of KOH (1M). Then 0.3 ml Triton x-114 (5%v/v) was added, and mixed well, and the volume was completed with distilled water. Then all the flask contents were transferred to 10-ml centrifuge tubes and kept for 10 min. In the thermostatic water bath adjusted at 40°C . The two phases were separated using a centrifuge (1500 rpm, 20min), and thereafter cooled in an ice bath, then the aqueous phases were decanted, and the surfactant-rich phases those contains the azo dye was dissolved in 3 ml of ethanol, and the absorbance of the dye at 448 nm was measured against the blank prepared under the same conditions.

Analysis of TbS its syrup preparations

Each 5 ml of syrup contains (1.25 mg of TbS). An accurate volume (20 ml) was transferred into a 50 mL volumetric flask. The solution was filtered by using Whatman filter paper No.41 to prevent any suspended material, and diluted to the mark with distilled water to obtain 100 $\mu\text{g/ml}$. Suitable volumes of this solution were taken to get 1, 3, and 5 $\mu\text{g/ml}$ in the final volume of 10 ml, then followed the general assay procedure.

RESULTS AND DISCUSSION

The preliminary investigation shows that TbS reacted with diazotized 2,4-DNA in a basic medium forming an azo dye product in the presence of Triton x-114. The resulting product has maximum absorption at 448 nm against reagent blank, Fig. (1).

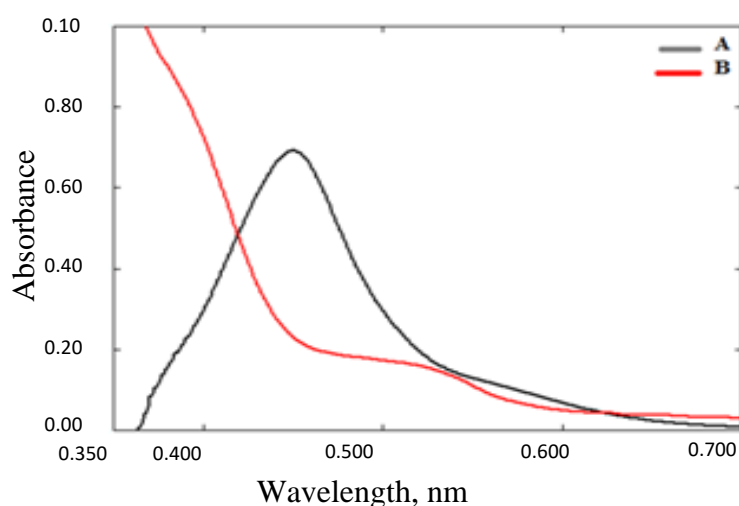


Fig. 1: Absorption spectra of azo dye product containing 2 µg/ml TbS against reagent blank in the presence of Triton x-114 (A) and blank versus distilled water (B).

Optimization of conditions

The effect of different conditions on azo dye formation reaction and absorbance intensity was studied, using 2.0 µg/ml TbS in a final volume of 10 ml and the absorbance was measured at 448 nm.

Effect of base

Different bases, such as NaOH, KOH, Na₂CO₃, and NaHCO₃, of 1M concentration are examined in the formation of azo dye product. As seen in Fig. (2), KOH was given high sensitivity. However; 1ml of 2M KOH are the best concentration and volume Fig. (3: a, b), which are recommended in subsequent experiments.

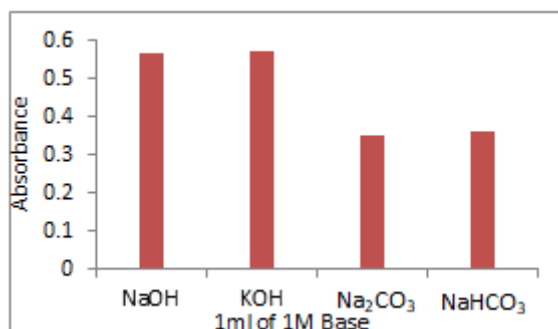


Fig. 2: Effect of base type on the absorbance of product.

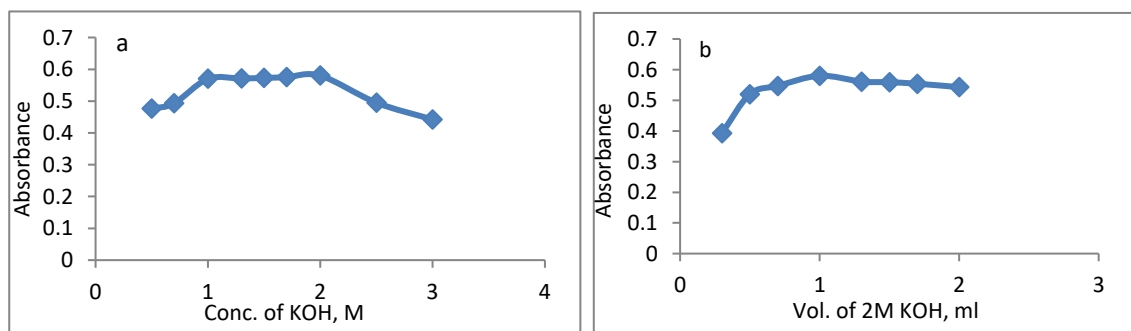


Fig. 3: Effect of KOH concentration (a) and volume (b).

Effect of concentration and volume of surfactant triton x-114

The impact of the Triton x-114 concentration and volume on the extraction efficiency was studied. The efficiency of extraction was increased with increases the surfactant concentration and was gave maximum absorbance at concentration 5% v/v and then decreases. However; it was found that 0.3 mL of surfactant gave maximum sensitivity, which was recommended in this method, Fig. (4).

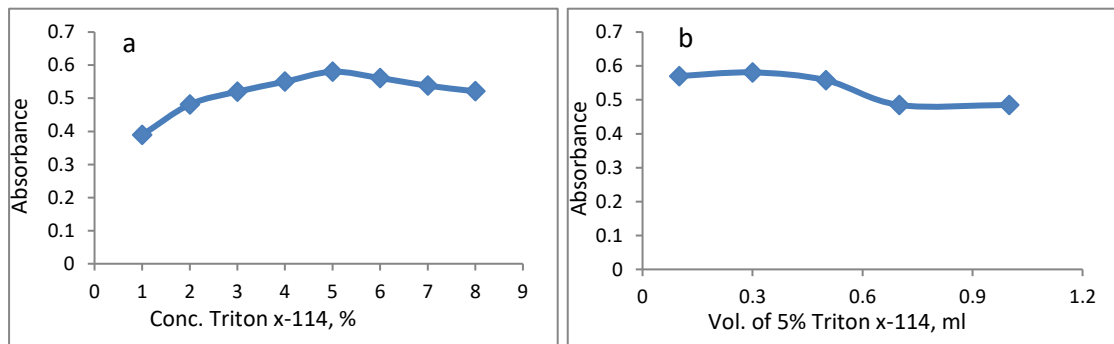


Fig. 4: Effect of Triton x-114 concentration (a) and volume (b).

Effect of addition sequence

The absorption of colored azo dye product is affected by the sequence of additives used in the reaction components. The results as shown in (Table 1) indicate that sequence I provides the maximum absorbance for the colored product. Therefore, this sequence has been followed and confirmed in the following experiments.

Table 1: Effect of sequence addition on the absorbance of azo-dye product

Order number	Reaction components	Absorbance
I	R+S+B+Triton X-114	0.582
II	S+B+R+Triton X-114	0.012
III	B+R+S+Triton X-114	0.000

R (diazotized 2,4-DNA), S (Terbutaline sulphate), B (KOH)

Effect of temperature and time of extraction

Optimizing the extraction temperature and incubation time is crucial for achieving the efficiency for phase separation and ease of preconcentration. The effect of temperature on the extraction of colored complexes should be investigated. An incubation temperature between R.T (20°C) and 70°C for 10 minutes was investigated. At 40°C, the maximum absorption of the product was selected Fig. (5). To achieve equilibrium between the aqueous and surfactant-rich phases, the CPE method typically requires sufficient time. The incubation time on extraction efficiency was examined at 40°C for 5–60 min. The process of separation required only 10 min. For incubation Fig. (6). A centrifugation time of 20 minutes, at 2000 rpm, was chosen as optimal because complete separation occurred within this period Fig. (7).

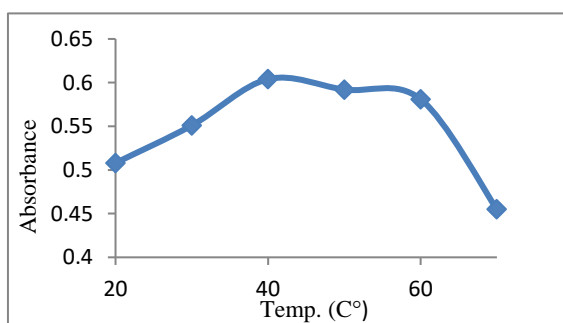


Fig. 5: Effect of temperature in extraction.

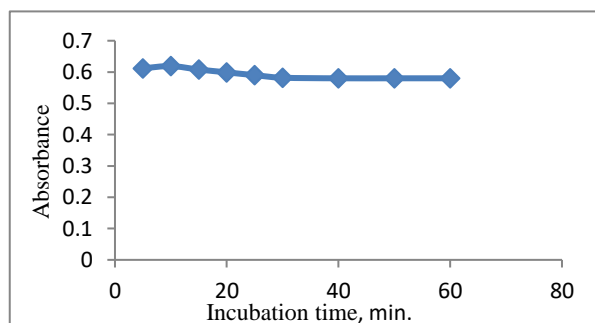


Fig. 6: Effect of incubation time.

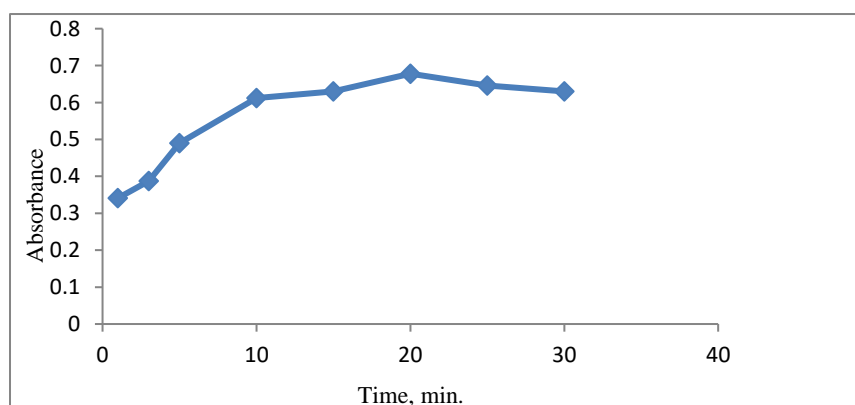


Fig. 7: Effect of centrifugation time.

Azo Dye stability

The stability of the resulting azo dye product (after extraction by Triton x-114) with different time periods. The absorbance of the final product, containing 2.0 µg/ml TbS, was measured at 448 nm versus the blank. It was found that the product was stable for 80 min, Fig. (8).

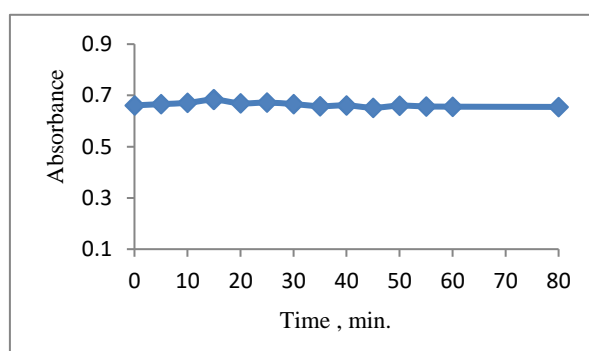


Fig. 8: Stability of azo dye product.

Quantification

Depending on the above optimum conditions, the absorbance of TbS increased linearly as the its concentration increased, the calibration curve was plotted using a series of standard TbS solutions, Fig. (9). The method adheres to Beer-Lambert's law within concentration range 0.1-13 µg/ml with the molar absorptivity of $1.6 \times 10^6 \text{ L. mole}^{-1} \cdot \text{cm}^{-1}$ indicating the method has high sensitivity. The suggested method yielded a correlation coefficient greater than 0.9992, indicating excellent linearity. Intercept, slope, LOD, LOQ, and the Sandell's sensitivity are assessed and demonstrated in (Table 2).

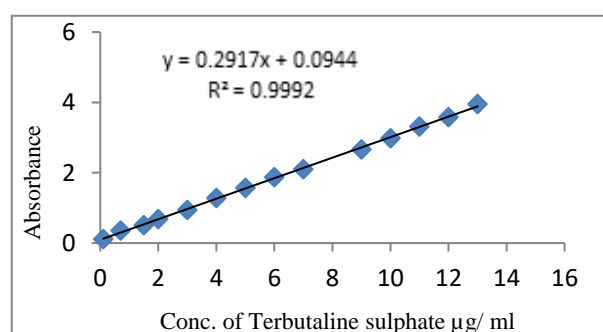


Fig. 9: Calibration graph for determination of TbS.

Table 2: Optical characteristics and statistical data for the proposed method.

Parameter	Terbutaline sulphate
λ_{\max} (nm)	448
Linearity range ($\mu\text{g/ml}$)	0.1-13
Molar absorptivity ($\text{L.mol}^{-1}.\text{cm}^{-1}$)	1.6×10^6
Sandell's sensitivity ($\mu\text{g/cm}^2$)	0.0034
LOD ($\mu\text{g/ml}$)	0.042
LOQ ($\mu\text{g/ml}$)	0.140
Intercept	0.0944
Slope	0.2917
Determination coefficient (R^2)	0.9992

Accuracy and precision

At four different concentrations of TbS with five replicates for each were determined, the results obtained in (Table 3) indicating the method is accurate and precise.

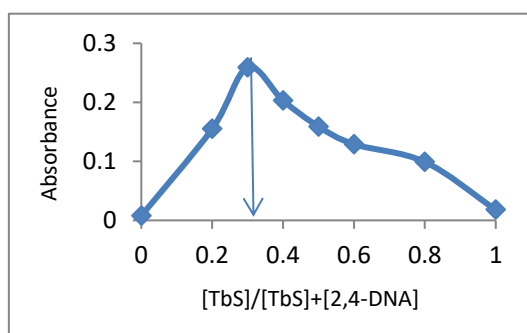
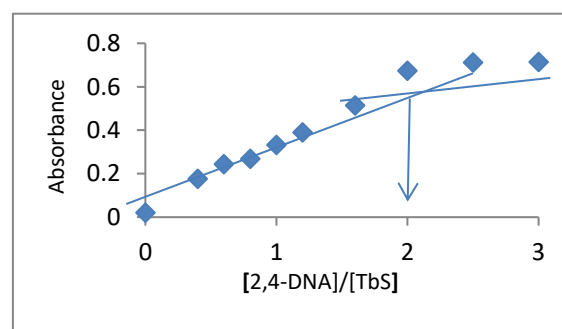
Table 3: Accuracy and precision of the present CPE method for TbS

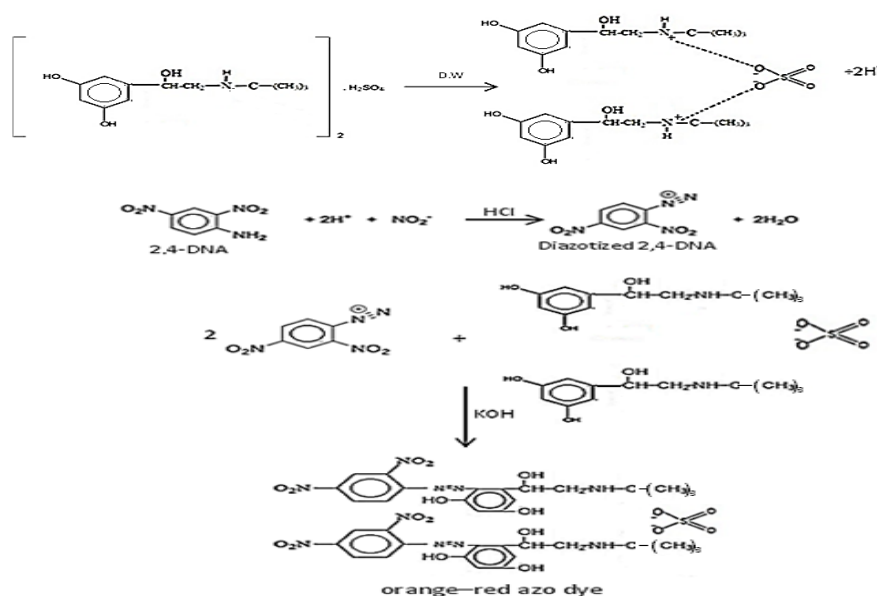
Drug	Drug conc. ($\mu\text{g/ml}$)		Recovery* (%)	Average recovery (%)	RSD* (%)
	Amount present	Amount found			
Terbutaline sulphate	1	1.02	102.00	98.91	1.60
	3	2.86	95.33		0.83
	5	5.01	100.20		0.23
	7	6.87	98.14		0.30

*Mean of five determinations

Stoichiometric, stability constant and mechanism of Azo Dye

The composition of azo dye formation between TbS drug and diazotized 2,4-DNA (1.8×10^{-4} mole/l for each) was studied by continuous variation (Job's method) and mole-ratio (De-Levie 1997). Fig. (10, 11) show that the azo-dye formation in the ratio 1:2 TbS: diazotized 2,4-DNA. Since TbS contains two molecules of TbS, therefore the actual ratio is 1:1 TbS: 2,4-DNA. Depending on this ratio, the conditional stability constant of azo-dye product was calculated, and was to be $3.7 \times 10^5 \text{ l. mole}^{-1}$ indicating the high stability of the product. However; the mechanism has been proposed in scheme (1).

**Fig. 10: Continuous variation for Azo- Dye product.****Fig. 11: Mole-ratio for Azo-Dye product.**



Scheme 1: Propose mechanism for the formation of azo dye product.

Interferences

To prove the efficiency of the proposed method in the determination of TbS in pharmaceutical Preparation as syrup, the standard addition procedure was applied. The results in Fig. (11) and in (Table 5) indicating that the proposed method is selective and could be applied to pharmaceutical formulation successfully.

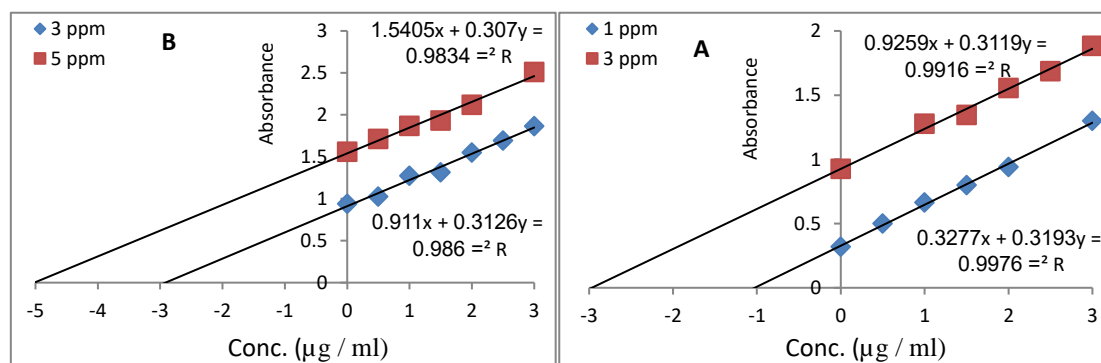


Fig. 11: Plots of standard addition procedure for determination of TbS in syrup
A - Egyptian product. **B - Syrian product.**

Validation of the method

The suggested method used to be utilized for the estimation of TbS syrup in its pharmaceutical formulation, produced by two companies. The results confirmed accurate and good agreement with the certified value. Also, the results of the proposed method had been statistically examined by applying student's t-test for accuracy, by applying the following equation (Skoog *et al.*, 2004):

$$t_{\text{exp}} = \frac{|\mu - \bar{X}|}{S} \sqrt{n}$$

Where:

μ : Certified amount of drug
 S : Standard deviation

\bar{X} : Average of recovered amount
 n : Number of replicates

The results, cited in (Table 4), indicate that the experimental t-test at the 95% confidence level for 4 replicates, are less than the theoretical value ($t=3.18$), indicating there is no significant difference between the certified value and the determined amount.

Table 4: Validity of the proposed method in syrup formulation.

Pharmaceutical formulation	Certified value	Drug amount present ($\mu\text{g/ml}$)	Drug amount found* ($\mu\text{g/ml}$)	Recovery ^a (%)	Average recovery (%)	Average recovery (mg)	t-test
ALL- VENT Syrup ^b	1.25 mg/ 5 ml	1	0.98	98.00	98.24	1.22	2.86
		3	2.86	95.33			
		5	5.07	101.40			
Bilcavon Syrup ^c	1.25 mg/ 5 ml	3	2.89	96.33	98.38	1.23	2.84
		5	5.02	100.40			
		7	6.89	98.42			

^aAverage of four determinations.

^b Produced by BORG Pharmaceutical IDN company, Egypt.

^c Produced by UITRA Medica Pharmaceutical Industries, Syria.

Table 5: Standard addition method for determination of TbS by the proposed method

Pharmaceutical formulation	Certified value	Amount present ($\mu\text{g/ml}$)	Recovery* (%)	Drug content found (mg)	
				Present method	Standard addition method
BILCAVON Syrup Syria	1.25mg/5 ml	3	97.00	1.20	1.21
		5	100.20	1.25	1.25
ALLVENT Syrup Egypt	1.25mg/5 ml	1	102.00	1.22	1.27
		3	98.66	1.19	1.23

*Average of three determinations.

Comparison of the current CPE method for estimation of TbS with other literature Methods

The developed approach for assay of TbS was compared with other spectrophotometric methods stated in the literature. The comprehensive comparison has been documented in (Table 6). The comparison showed that the proposed method has high sensitivity and low detection and quantitation limits, in addition to being consistent in terms of accuracy, compatibility, and analysis of the drug compound in its pharmaceutical preparations.

Table 6: Comparison of the proposed method with other literature methods

Analytical Parameters	Present method	Literature methods		
		(Jabar <i>et al.</i> , 2022)	(Smith <i>et al.</i> , 2010)	(Dhamra <i>et al.</i> , 2014)
Reaction type	Azo dye formation	Nucleophilic compensation	Ternary complex formation	Ion-pair complex formation
Reagent	2,4-DNA	9-Chroacridine	Antipyrine + Fe^{+3}	Eosin Y
λ_{max} (nm)	448	589	550	545
Linearity, ($\mu\text{g/ml}$)	0.1 - 13	0.1 - 6	4-20	0.5-10
Molar absorptivity ($\text{L. mol}^{-1} \text{ cm}^{-1}$)	1.6×10^6	1.075×10^5	1.190×10^4	3.169×10^3
Temp. ($^{\circ}\text{C}$)	40	R. T	-	R. T
LOD, ($\mu\text{g/ml}$)	0.04	0.0983	0.0811	0.03
LOQ, ($\mu\text{g/ml}$)	0.14	0.2978	0.246	0.103
Recovery %	98.91	99.6	99.87-100.66	101.42
RSD %	≤ 1.60	1.57	0.93	≤ 0.72
Application	Syrup	Tablet	Tablet	Tablet

CONCLUSIONS

A CPE technique has been described for the spectrophotometric determination of TbS in its pure and syrup formulation. The method is dependent on the coupling of TbS with the diazotized 2,4-DNA in the basic aqueous medium producing an azo dye product which was extracted by Triton x-114, and measured at 448 nm. The method was characterized by sensitivity (Molar absorptivity = $1.6 \times 10^6 \text{ l.mol}^{-1}.\text{cm}^{-1}$), accuracy (Recovery % = 98.91), and precision (RSD = ≤ 1.60). The method was successfully applied in the determination of TbS in pharmaceutical preparations as syrup from different origins, as it was found that the results of the method were in good agreement with the original content of the pharmaceutical compound and with the standard addition method (which demonstrated the absence of interference by excipient materials).

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تطبيق استخلاص النقطة السحابية في التقدير الطيفي لكبريتات التريبوتالين باستخدام تفاعل الأزوتة والاقتزان

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الخلاصة

تم استخدام طريقة استخلاص النقطة السحابية في التقدير الطيفي لكبريتات التريبوتالين (TbS) بشكله النقي وفي مستحضره الصيدلاني، تميزت الطريقة بالدقة والتوافق والحساسية الجيدة. اعتمدت الطريقة على تفاعل TbS والكاشف 4،2-ثنائي نيتروانيلين المؤزوت في الوسط القاعدي. تم قياس امتصاص صبغة الأزو البرتقالية الناتجة، التي تم استخلاصها بواسطة عامل الشد السطحي ترايتون x - 114، عند الطول الموجي 448 نانوميتر. تمت دراسة الظروف المثلى لفصل الطور الغني. أمكن تطبيق قانون بير في مدى التركيز 0.1-13 ميكروغرام/مللتر. بلغ الامتصاص المولاري 1.6×10^4 لتر. مول⁻¹سم⁻¹. تم حساب حد الكشف (LOD) والحد الكمي (LOQ) ووجد أنهما 0.04 و 0.14 ميكروغرام/مللتر على التوالي، ومعدل نسبة الاسترجاع 98.91%، وكان الانحراف القياسي النسبي (RSD) $\geq 1.6\%$. كما وجد من خلال دراسة طبيعة الناتج أن صبغة الأزو الناتجة تتكون بنسبة 1:1 من TbS إلى 4،2-ثنائي نيتروانيلين المؤزوت. تم تطبيق الطريقة بنجاح لتقدير TbS في الشراب وكانت خالية من التداخل بواسطة السواغات، وبمعدل نسبة استرجاع 98.91%. كما تم اقتراح ميكانيكية التفاعل.

الكلمات الدالة: المطياف الفوتومتري، النقطة السحابية، 4،2-ثنائي نيتروانيلين، كبريتات التريبوتالين.