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Colorimetric Determination of Salbutamol Sulfate using Spectrophotometry-Continuous Flow Injection Technique in Bulk Powder and Pharmaceutical Forms

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Abstract

Simple, precise and economic batch and flow injection analysis (FIA)-spectrophotometric methods have been established for the determination of salbutamol sulfate (SLB) in bulk powder and pharmaceutical forms. Both methods based on diazotization coupling reaction of SLB with another drug compound (sulfadimidine) as a safe and green diazotization agent in alkaline medium. At 444 nm, the maximum absorption of the orange azo-dye product was observed. A thorough investigation of all chemical and physical factors was conducted for batch and FIA procedures to achieve high sensitivity. Under the optimized experimental variables, SLB obeys Beer's law in the concentration range of 0.25-4 and 10-100 µg/mL with limits of detection of 0.09 and 2.51 µg/mL for batch and FIA procedures respectively. The high reproducibility of less than 1% (n=5) for both methods confirmed the applicability of these methods. Using F and t tests, a statistical comparison of the recommended approaches with the standard spectrophotometric method revealed no significant differences in accuracy or precision.

Keywords: Salbutamol, Sulfadimidine, Flow injection analysis, Diazotization reaction.

التقدير اللوني لكبريتات السالبيوتامول باستخدام تقنية الحقن الجرياني المستمر في الاشكال النقية والصيدلانية

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الخلاصة

تم وضع طرق بسيطة ودقيقة واقتصادية وهما طريقة الدفعة والحقن الجرياني المستمر، لتقدير دواء كبريتات السالبوتامول (**SLB**) في الشكل النقي والاشكال الصيدلانية. اعتمدت كلا الطريقتين على تفاعل الازوتة والازدواج للدواء مع دواء اخر وهوَ (السلفاديميدين) ككاشف أزوتة آمن في الوسط القاعدي. عند ٤٤٤ نانومتر والتي عندها تم الحصول على اعلى امتصاصية لناتج صبغة-الازو البرتقالية. تم التحقق من كل العوامل الكيميائية والفيزيائية لطريقتي الدفعة والحقن الجرياني للحصول على اعلى حساسية. وتحت الظروف التجريبية المثلىٰ للمتغيرات اطاع الدواء قانون بير عند مدى التراكيز ٠,٢٥-٤ و ١٠-١٠٠ مايكروغرام/مل وحدود كشف ٠,٠٩ و ٢,٥١ مايكروغرام/مل لطريقتي الدفعة والحقن الجرياني على التوالي. وكانت نسبة الانحراف القياسي النسبي اقل من ١٪(**n=5**) لكلا الطريقتين والذي اكدت امكانية تطبيق كلا الطريقتين. وباستخدام اختباري ال(**F**) وال (**t**) تم عمل مقارنة احصائية للطريقتين المقترحتين مع الطريقة الطيفية القياسية والتي كشفت انه لا يوجد فرق واضح في الدقة والتوافقية لكلا الطريقتين.

الكلمات المفتاحية : سالبيوتامول ، سلفاديميدين ، التحليل بالحقن الجرياني ، تفاعل الأزوتة.

Introduction

Salbutamol sulfate, also known as Albuterol sulfate is chemically known as (RS)-1-(4-hydroxy- 3- hydroxy methyl-phenyl)-2-(tert-butylamino) ethanol sulfate, is Beta 2 adrenergic receptor agonist bronchodilator drug have many uses such as treatment of patients with asthma [(1)]. By reviewing the literature, it was found that there are many methods applied for estimation of SLB in different samples such as Liquid chromatography-mass spectrometry (LC-MS) [(2, 3)], capillary electrophoresis [(4)], HPLC [(5, 6)], spectrophotometry [(7-9)], flow injection analysis [(10, 11)], and voltammetry [(12, 13)].

Most of these methods are indirect or have drawbacks, such as reliance on expensive techniques, time demanding, and inappropriate for routine drug analysis [(14-16)] . As a result, it is essential to create a simple, quick, and low-cost approach for estimating SLB in commercial dosage forms. Spectrophotometric methods have been widely used in drug analysis; however, one of the most notable limitations of these approaches is the use of some hazardous chemical reagents for colorimetric reactions. As a result, replacement of these reagents with safer compounds like drugs is valuable option.

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FIA has a higher sampling rate, uses fewer chemicals, has better precision, and is more versatile than batch approaches. Because of the aforementioned benefits of FI, pharmaceutical analysis and quality control applications have seen a steady increase in interest. In the present work a drug compound was used as safe diazotization coupling reagent for estimation SLB using direct batch and FIA methods. Sulfa drugs frequently contain multiple reactive amino compounds, one of which is sulfadimidine (SDM), which is utilized as a colorimetric reagent in this study to estimate SLB.

Experimental

Instruments

Single beam spectrophotometer (Shimadzu UV-Visible 1240) was used for scan and absorbance measurements. The flow injection manifold composed mainly from 1 cm flow cell (50 µL), peristaltic pump type Ismatec (CH–8152, Switzerland) and injection valve (Rheodyne, USA) used for injection micro liters of the sample. Reagent solutions were continually pumped through flexible vinyl tubes while being mixed in a reaction coil (RC) consisting of Teflon tubes (0.5 mm i.d.). With the use of a dual-channel manifold (Figure 1); diazotized sulfadimidine (DSDM) was delivered through the first channel, while the second channel transported the NH_4OH solution. Through the second channel, through the injection valve, the SLB drug solution was injected into the DSDM reagent stream and subsequently mixed with the ammonium solution inside the RC. The peristaltic pump was utilized for pumping the solutions and the azo-dye product's absorbance was measured at the manifold's end.

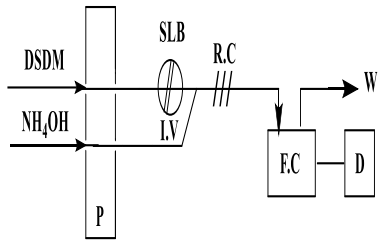


Figure 1. Continuous FIA manifold (DSDM, diazotized sulfadimidine; I.V, injection valve; P, Pump; SLB, Salbutamol sulfate; R.C, reaction coil; D, detector; F.C, flow cell; W, waste).

Chemicals and reagents

Pharmaceutical grade SLB and SDM (purity 99.9%) were supplied from Iraq's state drug industries company (Samara-Iraq). Butalin® tablets, labeled to contain 2 mg SLB, manufactured by Julphar industries-UAE and purchased from local pharmacies. Ammonia, sodium nitrite and HCl were purchased from BDH.

Solutions

- Salbutamol sulfate solution (500 µg/mL): A standard solution of SLB was prepared by dissolving 0.05 g of pure drug in 100 mL distilled water.
- Diazotized Sulfadimidine (0.01M): In 100 mL volumetric flask, 1mL of SDM standard solution (333 mg/mL) was transferred. After that a 3 mL of 1 M of HCl was added while keeping the temperature of the solution at 0-5 Cº in ice–bath. A weight of 0.069 g amount of $NaNO_2$ was added with shaking for 5 min and then completed the volumetric flask with distilled water.
- Hydrochloric acid (1M) and ammonium hydroxide (2M) aqueous solutions were laboratory prepared by simple dilution of concentrated hydrochloric acid (36.4% w/w) and ammonia solution (25% w/w) respectively and then standardized.

Solutions of marketed formulation

After carefully weighing and grounding commercially available SLB tablets, an amount of tablets' powder equivalent to 0.05 g of pure drug was taken and dissolved in 50 mL of distilled water. The solution was then stirred vigorously for 15 minutes before being filtered into a 100 mL volumetric flask and diluted with distilled water.

General procedure of batch method

Series volumes of standard solution of SLB covers the range of concentrations of 0.25-4 µg/mL were transferred into 10 mL volumetric flasks. To each flask, 1.0 mL of DSDM (0.01M) and 4 mL of NH_4OH (0.1M) solution were transferred then diluted with distilled water and mixed well. The reaction reaches to maximum intensity and stability after 10 min, and then the absorbance was measured at 444 nm (at 25 Cº) against reagent blank. The SLB's amount was calculated using the calibration graph's regression equation. A concentration of 2 µg/mL SLB was utilized in all batch optimization tests.

General procedure of FIA method

A 150 µL of SLB standard solution (range from 10-100 µg/mL) was injected through the injection valve utilizing a syringe. Samples of SLB were injected into 0.01M of DSDM stream. The resultant solution was mixed with 0.05 M NH_4OH solution in the reaction coil. Peristaltic pump propelled the solutions (flow rate of 2.87 mL/min) and the absorbance of the resulting orange product was monitored at 444 nm. A 50 µg/mL of SLB was employed in the investigation of the FI system's optimum conditions.

Results and Discussion

The diazotization method is used for the determination of compound containing the primary aromatic amine group [17]. Most of these compounds are toxic, so it is preferable to use a pharmaceutical compound as a chromogenic reagent to make the

methods less expensive and safer. In the present work, an orange dye produced from the coupling of SLB with diazotized SDM (drug compound) was studied using batch and continuous FIA methods. All the parameters that enhance the sensitivity of the reaction and consequently the assay of SLB drug were studied. The influences of the chemical and physical parameters were carefully studied.

Absorption spectra and the mechanism of reaction

The maximum value of absorption of azo-dye formed was estimated at 444 nm versus the blank in alkaline medium (Figure 2).

The supposed mechanism of the reaction was summarized in scheme 1. The aromatic amino group in sulfadimidine drug (the reagent in this study) is easily converted to diazonium salt during the diazotization reaction with nitrous acid. The diazonium salt then is coupling with phenolic drug (SLB) in alkaline medium. Using equimolar concentrations (4.2×10^{-4} M) of the drug and DSDM under the specified optimal conditions, the stoichiometry of the SLB-SAD dye was inspected by Job's and molar ratio methods [18,19]. A stoichiometry of 1:1 (SLB: SAD) was found with ε (molar absorptivity) value of 9.09×10^{3} L/mol cm.

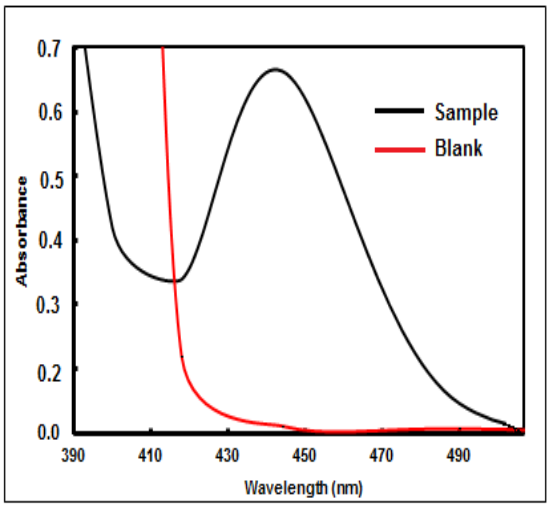
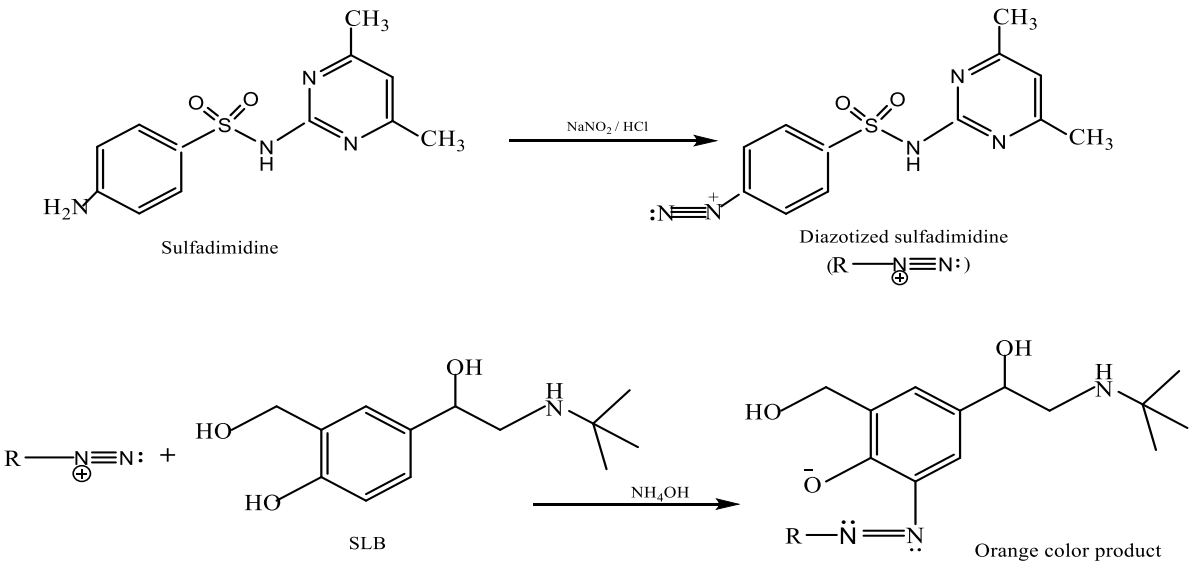


Figure 2. Absorption spectra of (a) azo-dye product result from the reaction SLB with DSDM/NH_4OH measured versus the blank and (b) the blank versus distilled water.



Scheme 1. Proposed reaction mechanism

Optimization conditions of batch method

When DSDM is mixed with SLB in the presence of ammonium hydroxide solution, an orange azo-dye product form very instantly. The azo-dye was found to absorb at 444 nm, Fig. 2. The absorption of the orange dye was shown to be influenced by a number of factors, which were investigated consequently.

The influence of altered volumes of 0.01M of DSDM (from 0.5 to 3 mL) and 0.1 M NH_4OH (from 0.5 to 4 mL) were studied. Maximum absorbance was obtained using 1 mL of 0.01M DSDM and 4 mL of 0.1 M ammonium hydroxide as shown in Figure 3.

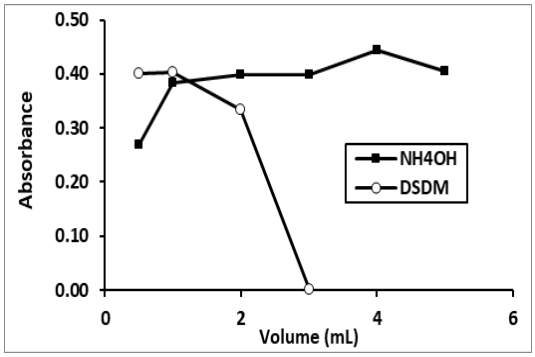


Figure 3. Effect of the volumes of DSDM and NH_4OH

After 10 minutes from the start of the reaction, the product's absorbance was stable and remained constant for more than 30 minutes. The azo-dye product is formed and remains stable at room temperature, but as the temperature rises, the azo-dye decomposes; thus, room temperature (25 ^{0}C) is the optimal reaction temperature. Also, different reagents addition orders were examined and it was found that the following order (DSDM+SLB+NH_4OH) was effective in achieving the desired findings (Fig. 4) and was utilized in all subsequent tests.

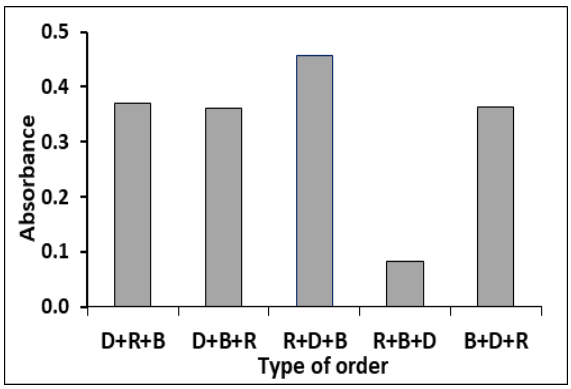


Figure 4. Order of addition (D=Drug, B=Base, R= diazotized reagent)

Optimization conditions of FIA method

Manifold design

The effects of all chemical and physical variables on the sensitivity estimation of SLB using the FIA approach were investigated. The FIA manifold is the most essential parameter that must be optimized. To execute multiple reaction paths for SLB drug with DSDM in alkaline medium, different types of manifold configuration (single and double channels manifolds) were studied. The two channels FI manifold provided the highest sampling frequency and maximal absorbance intensity. SLB was injected into DSDM stream, which then combined with NH_4OH using mixing coil as given in Figure1.

Chemical variables

The concentration effect of DSDM on the absorbance of dye was examined. Into the stream of various concentrations of diazotized reagent (0.005-0.05 M), a 150 µL of SLB was injected. The results (Fig. 5) indicated that a 0.01 M gave the best analytical signal and was chosen as optimum value. According to the previous studies, the reaction between SLB and DSDM must carry out in an alkaline media; which could be because the phenolic drug (SLB) is transformed to a more reactive phenoxide molecule. The influence of changing the concentration of NH_4OH using a range of (0.01-0.1 M) was studied. The best results were obtained using 0.05 M of ammonium hydroxide (Fig. 5) which was selected for the following experiments.

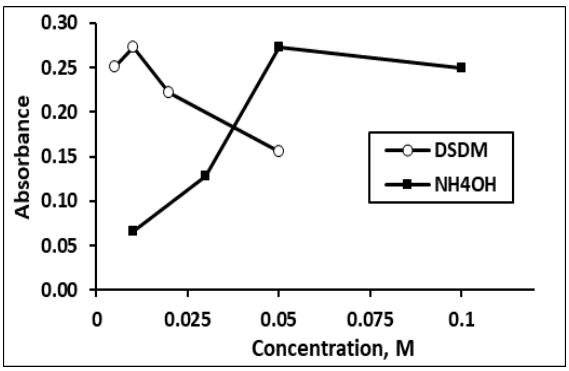
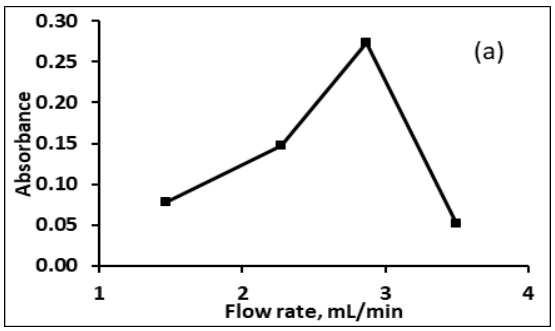


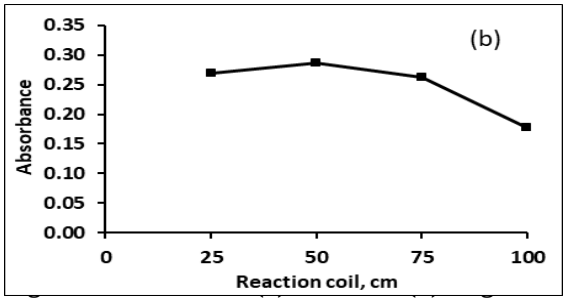
Figure 5. Effect of concentration of reagent and base

Physical variables

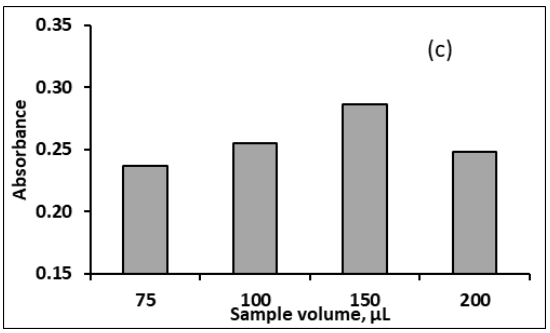
The flow rate has a great effect on the reaction sensitivity and sample frequency: Therefore, this parameter was studied by using different rates ranged between 1.47-3.5 mL/min under the optimum conditions. When shown in Figure 6a, the highest signal was attained at 2.87 mL/min, and then degreased gradually as the rate was increased due to increased dispersion. For that reason, a total flow rate 2.87 mL/min was selected as optimum rate. In the range of 25-100 cm, the influence of the mixing coil length was studied. A significant increase in absorbance (peak height) was detected with increasing the coil length up to 50 cm and then decreased (Fig. 6b). This could be because of the fast coupling reaction between SLB and DSDM, which eliminates the need to lengthen the reaction's steady time by increasing the RC length. Because increasing the length of the RC creates increased dispersion and peak broadening, 50 cm was chosen for the following tests.

The optimal injected volume of the sample was also tested using varied lengths of sample loop connected to the injection valve ranging from 75 to 200 µL, while keeping the other parameters constant. The results (Fig. 6c) showed that 150 µL produced the highest intensity, thus that was chosen as the ideal volume. The flow system provided a sampling frequency of 39 samples h^{-1}.





reaction coil, and (c) sample volume on intensity of azo-dye product.



Continued Figure 6.

Summarized of optimum chemical and physical parameters

Table 1 lists all of the researched chemical and physical factors that may affect the azo-dye product's sensitivity for batch and FIA techniques.

Table 1. Summary of studied parameters of batch and FIA methods

Parameter	Studied range	Selected value	
		Batch	FIA
Concentration of DSDM (M)	5×10^{-3}-5×10^{-2}	----	0.01
	5×10^{-4}-3×10^{-3}	0.001	----
Concentration of NH_4OH (M)	0.01-0.1	----	0.05
	0.005-0.05	0.04	----
Injected sample volume (µL)	75-200	----	150
Length of reaction coil (cm)	25-100	----	50
Flow rate (mL/min)	1.47-3.5	----	2.87

Methods Validation

Calibration graphs

At the optimized conditions (Table 1), a linear calibration graphs were obtained for the analysis of SLB drug utilizing batch and FIA systems using a series of SLB standard solutions. All analytical figures of merit were summarized in Table 2 including linearity, repeatability, limit of detection (LOD), and limit of quantification (LOQ). The slope, molar absorptivity, Sandell's sensitivity, and correlation coefficient for the calibration data were reported. Batch and FIA methods showed good linearity within the range 0.25-4 and 10-100 µg/mL of SLB, respectively with correlation coefficients of at least 0.998. In comparison with the two techniques mentioned, FIA is more convenient than the batch approach because of its greater linear range of calibration graph and high throughput samples (39 Sample/h). The FIA method is less sensitive than the batch approach, which could be owing to sample zone dispersion inside the carrier as well as reagent solutions arriving at the detector.

Accuracy, reproducibility and selectivity

By analyzing three different concentrations of SLB solutions using both approaches, the accuracy and reproducibility of the suggested procedures were assessed as relative error and relative standard deviation (% RSD), respectively (Table 3). Low relative error values (±3%) and good % RSD values (0.28-0.98%) point to the high accuracy and reproducibility of the present methods.

Table 2. Analytical performance of proposed methods.

Variables	Batch method	FIA method
Regression equation	y=0.2695x-0.0061	y=0.0039x+0.0723
Linear range (µg/mL)	0.25-4	10-100
Correlation coefficient, r	0.9981	0.9998
Limit of detection (s/n = 3) (µg/mL)	0.09	2.51
Limit of quantification (µg/mL)	0.29	8.36
Molar absorptivity ε (L/mol cm)	9.09×10^{4}	1.32×10^{3}
Sandell's sensitivity, S (µg/cm^2)	0.0037	0.2564
Through-put (h^{-1})	6	39
Slope, b	0.2695	0.0039
Intercept, a	-0.0061	0.0723
$S_{y/x}$	2.37×10^{-2}	3.17×10^{-3}
S_b	6.31×10^{-3}	4.34×10^{-4}
S_a	1.50×10^{-2}	2.66×10^{-3}

Table 3. Accuracy and precision for batch and FIA methods

Sample	Batch Method				FIA Method			
	Present Conc. (µg/mL)	Found Conc. (µg/mL)	RE (%)	(Rec.±RSD)% (n = 3)	Present Conc. (µg/mL)	Found Conc. (µg/mL)	RE (%)	(Rec.±RSD)% (n = 3)
1	1	1.03	3.00	103.00±0.76	25	24.90	-0.40	99.60±0.89
2	2	1.96	-2.00	98.00±0.28	50	50.18	0.36	100.36±0.63
3	3	3.04	1.33	101.33±0.98	75	75.69	0.92	100.92±0.57

RE. Relative Error, REC: Recovery, RSD: Relative Standard Deviation

The interference of some additives that may be added to the drugs for manufacturing needs was evaluated in order to assess the selectivity and applicability of the recommended methods in routine analysis of SLB in commercial tablets. To the 2 µg/mL of SLB solution, fiftyfold of each interference (starch, lactose, polyvinylpyrolidone, and magnesium stearate) was added and evaluated separately utilizing batch and FIA techniques. Recovery ranged (97-101%) revealed that tablet additives had little to no effect, indicating that these methods could be used for SLB quality control with high accuracy and precision.

Analysis of pharmaceutical formulations

The two methods were utilized for the assay of SLB in pharmaceutical formulations (tablets) and the results are given in Table 3. The obtained results are in good agreement with the declared content. Recovery studies for these tablets were used to evaluate the proposed procedures, and the findings showed that both approaches had outstanding recoveries values ranging from 95 to 98.8%. As demonstrated in Tables 4, the findings of the two procedures were compared to the results produced by the official method [20] for the SLB drug.The t and F-test values at 95% confidence limit [21] indicated that there are no considerable differences between batch, FIA and standard methods for the assay of SLB in dosage forms.

Table 4. Application of the batch, FIA and reference methods for the determination of SLB in pharmaceutical dosage form.

Dosage form	Proposed methods								Standard method			
	Batch method				nFIA method							
	Conc.(µg/mL)		Rec. (%)*	RSD (%)*	Conc.(µg/mL)		Rec. (%)*	RSD (%)*	Conc.(µg/mL)		Rec. (%)*	RSD (%)*
	Taken	Found			Taken	Found			Taken	Found		
Butalin® tablet (2mg)	1	0.99	99.00	0.36	25	24.46	97.84	0.91	5	5.01	100.20	0.33
	2	1.90	95.00	0.37	50	49.27	98.54	0.37	10	9.97	99.70	0.92
	3	2.89	96.33	0.42	75	74.09	98.79	0.71	15	14.87	99.13	0.86
SLB pure			100.78				100.29				99.98	
t (4.303)**	0.832				0.784							
F (161.4)**	1.077				7.602							

***For five determinations, Conc., concentration; **Theoretical value.**

Conclusion

The batch and continuous FIA methods proposed for the analysis of SLB in commercial dosage forms have the following characteristics: sensitivity, low cost, safe use of drug ingredient as reagent, and cover a wide variety of assays. The proposed methods were fully validated, with acceptable results for all of the method validation factors that were investigated. The FI process is suitable for analysis of SLB in marketed formulations and is faster than batch methods due to its high sampling frequency (39 samples/h). There are several spectrophotometric and FIA methods for determining SLB, however many of them are insensitive, use hazardous reagents, or are quite expensive. Experiments also showed that the results achieved using the two proposed methods are useful; therefore, these methods could be used as alternative methods for routine analysis of SLB in different samples.

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