Egypt. J. Chem. **Vol. 64,** No. 6 pp. 2913 - 2924 (2021)

Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Spectrophotometric Determination of Sulfadoxine Drug Use Cloud point and Flow Injection Methods in Pharmaceutical Formulations

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Abstract

New simple sensitive spectrophotometric methods are developed for the estimation of Sulfadoxine (SFD) in pure and pharmaceutical formulations. The first method includes a conversion primary amine to azo-dye by reacting sulfadoxine with sodium nitrite and hydrochloric acid followed by coupling with4-methoxyphenol in alkaline medium to obtain a stable reddish-orange colored dye at λ_{max}495nm. Concentration ranges 0.25-60 µg / mL, obeyed Beer's law, correlation coefficient was 0.9996, molar absorptivity was 0.589×10^{4}L.mol^{-1}.cm^{-1} and the detection limit was 0.157µg/mL. The second method was cloud point extraction (CPE) for estimating trace amount in an aqueous solution that produced from diazotization and measuring with a UV-visible spectrophotometer as are reddish-purple colored product at λ_{max}500 nm. The concentration range obeyed the Beer's law was 0.25-6µg / mL, correlation coefficient was 0.9998, molar absorptivity was 0.877×10^{5}L.mol^{-1}.cm^{-1}, detection limit was 0.023µg/mL, pre-concentration factor was 25 and Distribution coefficient(D) was 320.88. The last method was flow injection analysis it's simple for estimation the sulfadoxine. The concentration range was1-150µg / mL, obeyed Beer's law,the correlation coefficient was 0.9997, molar absorptivity was 0.273×10^{4}L.mol^{-1}.cm^{-1} and the detection limit was 0.375µg/mL. The offered methods were successful, useful for estimating sulfadoxine in traditional medications

Keywords: Sulfadoxine, diazotization, cloud point extraction, 4-methoxyphenol, Flow Injection Analysis

1. Introduction

Sulfadoxine is chemically 4-amino-N-(5,6-dimethoxypyrimidin-4-yl) benzene-1-sulfonamide as in fig. 1, belonging to the class of medication famous as sulfanilamides [1]. It is generally used for the usage or prevention of malaria and is also used as an anti-infective drug [2]. The enhanced clinical use of Sulfadoxine needed the development of new methods for estimating of Sulfadoxine. Literature review exposed different techniques for estimation of Sulfadoxine in traditional medications such as spectrophotometry techniques [3,4], liquid and gas chromatography [5], electrophoresis methods [6], potentiometeric methods [7, 8], and RP-HPLC technique's [9,10]. In general, ultra violet-visible spectrophotometry is the mostwide technique employed in quality control laboratories because of its inherent simplicity [11,12], sensitivity and cost-effectiveness [13,14] Therefore, developing selective and sensitive methods using visible spectrophotometry is of paramount importance [16,17]. Moderately a few visible spectrophotometric methods have been developed for the quantification of sulfadoxine in pharmaceuticals. However, many of these methods suffer from one or more disadvantages such as critical optimum conditions, heating, and extraction using an organic solvent, narrow linear dynamic range, poor selectivity and low sensitivity [18]. Flow injection is the best technique characterized as easy, inexpensive, quick and selective drug estimation [19], and the flow injection analysis (FIA) method has many interests, such as increasing sample throughput, low reagent use, reducing waste generation, and inexpensive equipment [20,21]. New methods for estimating sulfadoxine in conventional medicines are used in this work, based on eco-friendly and cheap methods that deliver quick, automated, reliable , accurate results that are applicable for use and do not require high work experience.

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Receive Date: 26 December 2020, Revise Date: 01 February 2021, Accept Date: 14 March 2021
DOI: 10.21608/EJCHEM.2021.55297.3164
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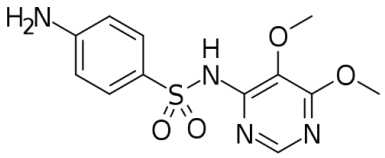

Fig. 1:Structure of Sulfadoxine

Instrumentation

In single-beam UV, visible spectrophotometer 295 (Lasany®- India). Fitted with quartz cells of 1 cm and 0.5 cm. An ultrasonic and thermostatic water bath combined with test extraction from Elma Hans Schmidbauer Gmbh and Co. KG. The layout of the three-channel flow injection manifold ALITEA,C4, made in Sweden) explained in Fig.2.

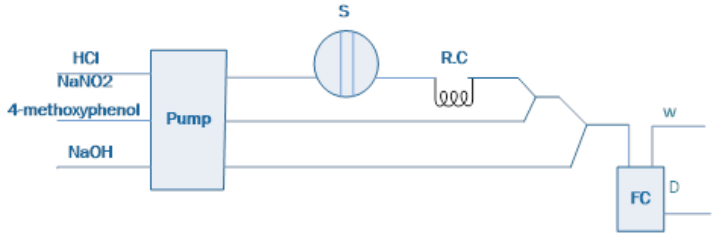

Fig. 2. Scheme of the employed flow system, P: peristaltic pump, R.C: reaction coil, S: sample injection, W: waste, FC: flow cell

Chemicals and Reagents

All chemicals were of analytical quality and were purchased from Merck. Sulfadoxine was obtained from the quality control laboratory (general company for the manufacture of medicines and medical supplies -Samarra).

Preparation of standard solution, Reagents.

Stock (1000 µg.m^{-1}) SFD solutions were prepared by dissolving 0.1g of pure sulfadoxine in 2ml of 0.4 M HCl and 100 mL of finished volume in a calibrated distilled water flask 4-methoxyphenol (1000 µg / mL) stock solution prepare by dissolving 0.1g of 4-methoxyphenol in distilled water and diluting it in a 100 ml volumetric flask to the mark. Preparation 25% NaOH,1%$NaNO_2$, 4% Urea ,10% Triton X-114, 5% w/v Na_2SO_4 and 0.01M of CTBA (Cetyl trimethyl ammonium bromide (0.3644 g in 100 ml distilled water) preparation.

The standard solutions of pharmaceutical Formulation

Sulfadoxine tablets supplied from the USA 500 mg Sulfadoxine & Pyrimethamine tablet and the Indian 200 mg Sulfadoxine & Pyrimethamine tablet were carefully weighed; the average weight was extracted from the individual tables. The equivalent weight of the individual tablet was dissolved in distilled water to ensure total solubility and applied up to 100 mL, after which the solution was filtered to prevent any suspended particles from being dissolved before use.

General procedure dizotization

The based method was developed to prepare Azo-dye by accurately introducing (1 ml of 1000 µg. mL^{-1}) sulfadoxine to 25 ml volumetric flask immersed in an ice bath at (0-5) ^{o}C, adding 0.75mLof (1:1) HCl, then gradually adding 0.5 ml of 1% $NaNO_2$, waiting 10 minutes, then adding 1 mL of (1000) µg / mL of 4-methoxyphenol, adding 2 mL of 25% NaOH and finally taking it to 25 mL of $NaNO_2$. The Azo-dye developed that has a reddish-orange color that gave an absorbance at a maximum of 495 nm against a blank reagent.

The general procedure of the cloud point extraction (CPE)

The calibration curve was constructed from different concentrations within the range of 0.25-6 µg / mL of azo-dye SFD prepared as indicated in the general procedure above 15 mL of formulated dye in centrifuge tubes, then 1 mL of Triton X-114 10 percent v / v was applied, followed by 2 mL of 0.01 M (CTAB), 2 mL of 5 percent w / v Na_2SO_4, and the complete tube of distilled water to the final volume. The solutions were put at room temperature under an ultrasonic bath for 2 minutes, followed by more ultrasonic at 55 ° C for 55 minutes. The resulting solutions were centrifuged at 4000 rpm for 5 minutes, then cooled for 10 minutes in an ice bath to stabilize the micellar layer at the bottom of the centrifuge tube. The supernatant was extracted and the layer of micelle was dissolved by adding 0.5 ml of ethanol. Absorbance calculation was performed against a reagent blank at λmax 500 nm.

The general procedure of flow injection of sulfadoxine

A 100 µl of SFD pure or pharmaceutical injected into carrier stream that produced by mixing three channel, the first channel used to carry the 5.89×10^{-3} M of 4-methoxyphenole, second channel including carrier of HCl and sodium nitrite by using T-shaped, this reaction was done via mixed well in 100 cm length reaction coil.The mixture allows passing through the injector and the resulted product reacted with a stream of 1M of 100 µl of SFD pure or pharmaceutical injected into the carrier stream formed by mixing three channels, the first channel used to transport 4-methoxyphenol (5.89×10-3) M, the second channel including HCl carrier and sodium nitrite using T-shaped, this reaction was well-mixed in a 100 cm long coil reaction. The mixture allows passing through the injector and the resulting substance reacted with a stream of 1 M of NaOH, the absorbance of the resulting Reddish-Orange estimated at λ_{max}495nm.

Results and Discussion: Diazotization method

The proposed method for converting SFD to azo-dye utilizing a diazotization method coupled with 4-methoxyphenol in alkaline media produces reddish-orange color with a wavelength at 495 nm. The spectra of the resulting azo-dye display shown in Fig.3.

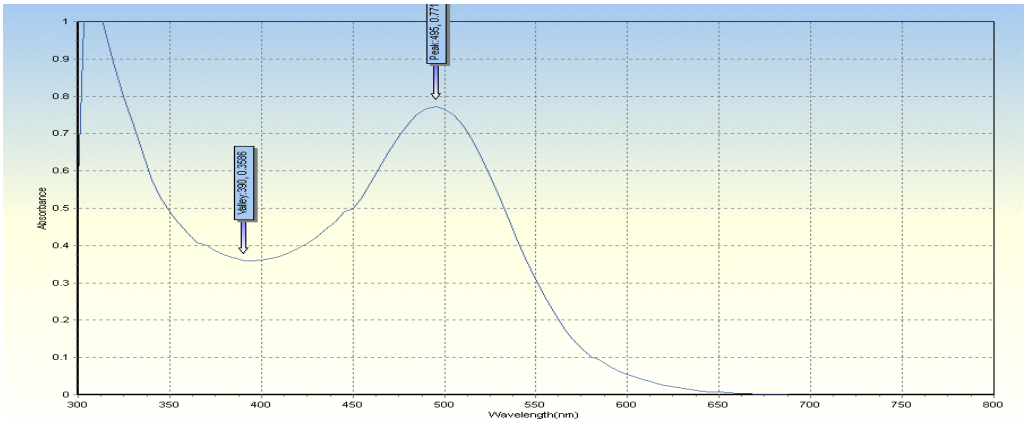

Fig. 3. Absorption spectrum for 50 µg/mL sulfadoxine with the reagent against the reagent blank under optimum conditions

The optimization of diazotization coupling reaction

Numerous (1:1) dilute acids (HCl, H_2SO_4, HNO_3, CH_3CO_2H) were checked for the acid type effect during the diazotization process, and the highest absorption was observed when HCl was used, as shown in Table 1.

Table. 1. Effect type of acids on absorbance

Type of acid	SMZ λ max 495nm
HCl	0.886
H_2SO_4	0.621
HNO_3	0.542
CH_3COOH	0.322

In the diazotization process, different amounts (0.25-2.5 mL) of HCl were examined, the highest absorption rate was measured using 0.75 mL for the SFD diazotization process in alkaline medium and the increase in the amount of acid used, decreased absorption as shown in Fig. 4. The quantity of $NaNO_2$ was calculated by changing the volume of (0.144 M of (1 % w / v) $NaNO_2$) used in the diazotization process from 0.25-2 mL and it was found that 0.5 mL produced the best strength of absorption as shown in Fig 5.

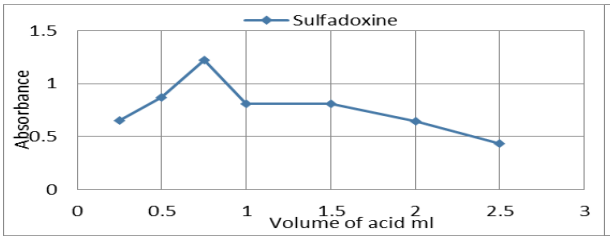

Fig.4. Effect volume of HCl/ mL

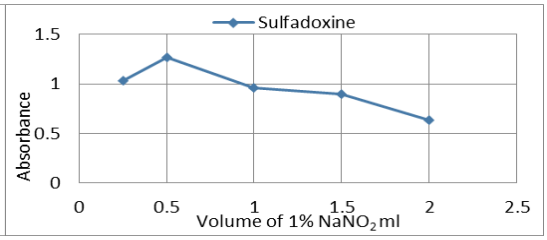

Fig.5. Effect volume of 1%$NaNO_2$

The reaction time was analyzed and it was observed that 10 minutes was adequate to achieve the maximum intensity of absorption as shown in fig. 6. A series of different volumes (0-4) mL of 4 % w / v urea, the results indicated that 1 mL is adequate to remove the excess of remaining acid as shown in Fig. 7, was performed to remove the excess of nitrous acid. Different base types (KOH, NaOH, Na_2CO_3, and NH_4OH) were investigated. When NaOH was used, the highest absorption intensity was gained. Also, different volumes of 6.25 M NaOH (1-3.5 mL) were tested to fix the exact volume of NaOH, 2 mL of 6.25 M NaOH gave the best results as shown in Fig.8.

Amino drug sulfadoxine react with nitrous acid to yield diazonium salts then coupling with phenolic reagent in alkaline medium to yield azo-dye shown in Fig.9.

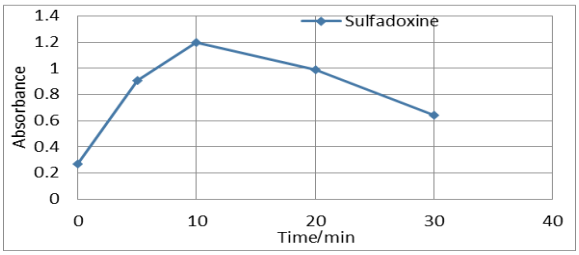

Fig. 6. Effect time/min

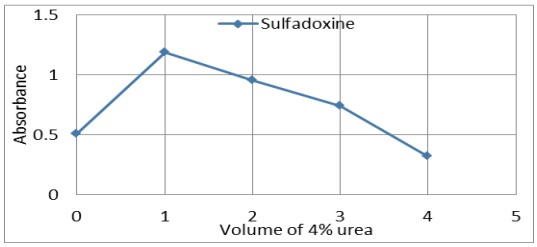

Fig.7. Effect volume of 4% Urea

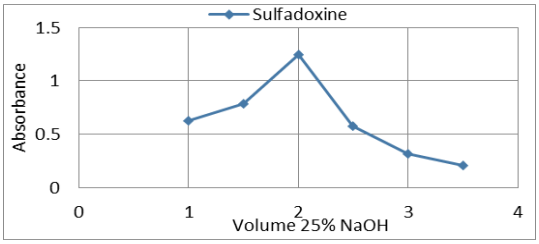

Fig.8. Effect volume of 25% NaOH

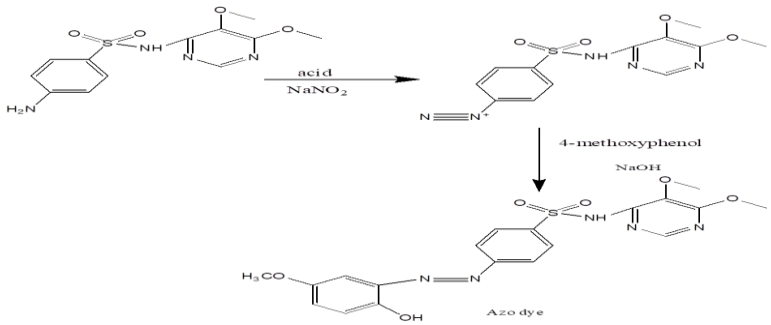

Fig. 9. The suggest mechanism of reaction SFD medication with 4-methoxyphenol colored step

Once the optimal conditions were obtained, a built-in calibration graph was investigated using the sequence of the standard solution of sulfadoxine and the linear regression equation, the correlation coefficient (R),

the slope (a) and the intercept (b) were calculated.
Calibration graph is examining in (Fig.10).

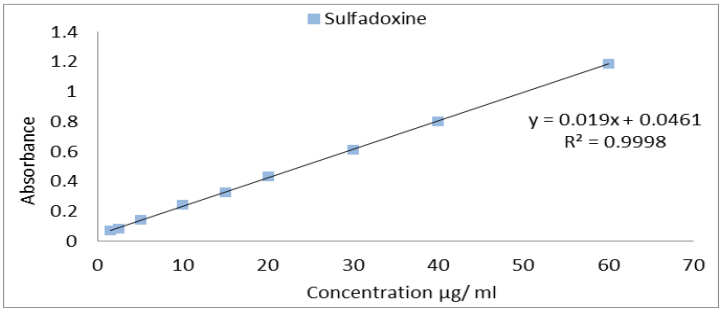

Fig. 10. calibration graph of sulfadoxine in diazotization method

Table 2. Characteristic parameter for the regression equation of the proposed diazotization method for sulfadoxine

Parameter	Sulfadoxine
λ max(nm)	495
color	Reddish-Orange
linearity rangeµg/mL	0.25-60
Molar absorptivity (L.mol^{-1} cm^{-1})	0.589×10^4
Sandell's sensitivity µg/cm^2	0.053
Correlation coefficient r	0.9996
Regression equation	Y=0.019x+0.0461
Slope(b)	0.019
Intercept(a)	0.0461
Analytical sensitivity µg/mL	0.044
Limit of detection µg/mL	0.157
Limit quantification µg/mL	0.526

Accuracy and precision

The accuracy and precision were studied for the proposed method, under optimum conditions using three altered concentrations and measured absorbance at a minimum for five readings per concentration. The RE (%) and RSD (%) values were less than1% that indicates the high precision, as shown Table 3 and 4.

Effect of interferences

In order to discover the analytical ability of the proposed procedure, the effects of certain common excipients also accompany drugs. The results presented in Table 5, indicated that no interference was found from any of the excipients studied in the determination of sulfadoxine.

Table 3. Data of accuracy and precision of the proposed method for the estimation of pure samples

Type of Medication	Amount of medications µg /ml		Relative Error %	Recovery %	Average Recovery%	RSD% (n=5)
	Taken	Found				
Sulfadoxine	5	4.970	-4.6	95.40		0.08
	10	9.99	-0.1	99.9	98.63	0.14
	15	15.10	0.6	100.6		0.19

Table 4. The accuracy and precision of the proposed method for the estimation of commercial pharmaceuticals

Type of Medications	Amount of medications mg		Relative Error %	Recovery %	Average Recovery %	RSD% (n=5)
	Taken	Found				
Sulfadoxine & Pyrimethamine tablet USA 500 mg	500	498.7	-0.26	99.74	99.92	0.20
		500.3	0.06	100.06		
		499.8	-0.04	99.96		
Sulfadoxine & Pyrimethamine Tablets Indian 200mg	200	200.7	0.35	100.35	100.06	0.90
		201.8	0.9	100.9		
		197.9	-1.05	98.95		

Table 5. Effect of interference compound on pure medication

Interferences compound	Recovery %of SFD
Sucrose	99.68
Lactose	100.12
Maltose	100.33
Fructose	99.58
Sodium Benzoate	100.23
Starch	99.78

Study of optimization of cloud point extraction for SFD medication

For the selection of the best quantity of triton X-114 A series of different volumes (0.25-2.5) mL of 10 percent triton X-114 add to the solutions of the dye substance for the cloud point extraction process, the results obtained are shown in Fig.11.The series of different volumes (0-3.5) mL of cationic surfactant is also studied to increase the hydrophilic characteristic of the micelle phase used to find the best volume of CTAB (Cetyl tri methyl ammonium bromide) to provide the best absorption, as shown in Fig. 12. As shown in Fig.13, the best electrolyte was Na_2SO_4 and 2 mL of the optimum volume needed to achieve the highest extraction efficiency and the highest distribution ratio. Confirm the successful separation and pre-concentration of SFD, the parameters of equilibration temperature and incubation were calculated as the most important steps in cloud point extraction. Adjust the temperature from 25 to 65 ˚C. The best temperature was 50 ˚C. Fig.14 shows the results.

Calibration graph of the cloud point extraction of SFD

After the optimization conditions, the CPE experimental calibration graph for SFD of the linear calibration graph began by plotting the different concentrations of SFD (0.25-6) µg/ mL against the absorbance, analytical data obtained from the calibration graph, the linear regression equation, the coefficient of correlation, slope and intercept, was obtained from the proposed cloud point extraction approach for SFD, Fig.15, and Table 6.

Accuracy and precision

Evaluate the precision and accuracy of the proposed procedure, using various concentrations under optimal conditions and calculating absorbance at a minimum of five readings per concentration. Determination of precision and accuracy by RE %, R% and RSD %, as shown in Tables 7and 8.

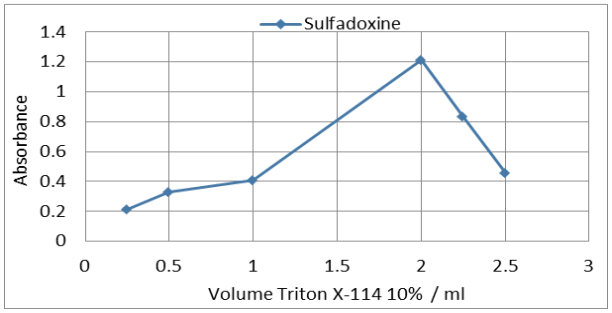

Fig.11. Effect volume of TritonX-114 / mL

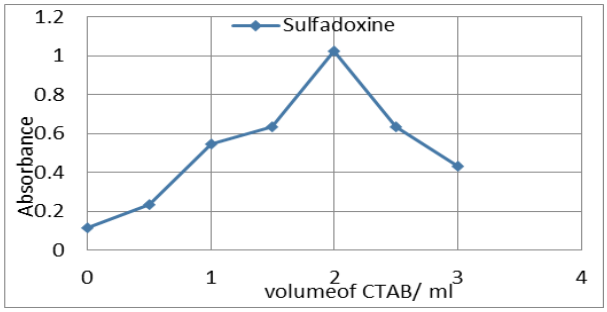

Fig.12. Effect volume of CTAB /mL

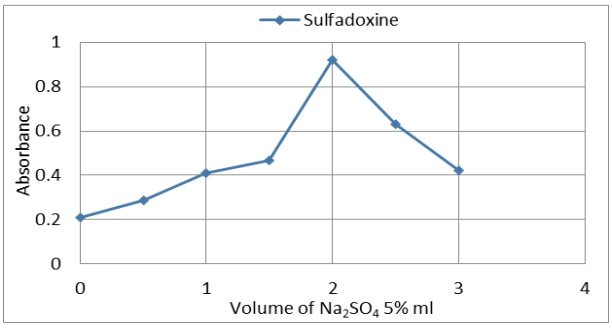

Fig.13. Effect volume of Na_2so_4 5% mL

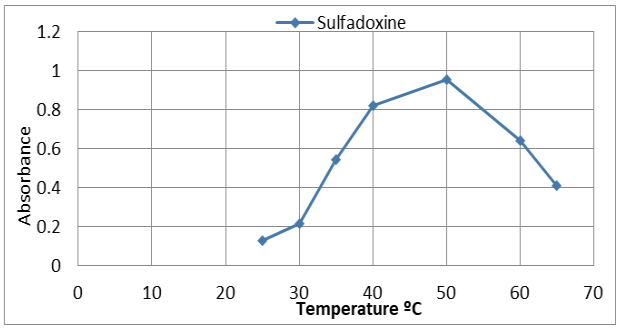

Fig.14. Effect of Temperature ºC

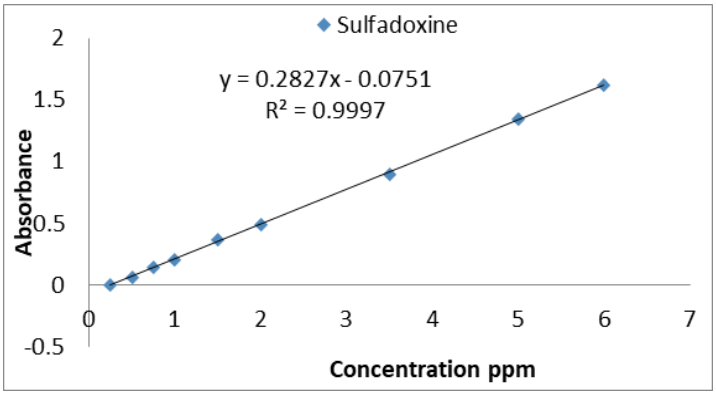

Fig. 15. Calibration graph of SFD by cloud point extraction

Table 6. Characteristic parameter for the regression equation of the proposed CPE of CFD

Parameter	Sulfadoxine
λ max(nm)	500
color	reddish-Purple
linearity rangeμg/mL	(0.25-6)
Molar absorptivity (L.mol^{-1}.cm^{-1})Ɛ	0.877×10^5
Sandell's sensitivity (μg/ cm^2)	0.004
Correlation coefficient(r)	0.9998
Regression equation	Y=0.2827x-0.0751
Slope(b)	0.2827
Intercept(a)	-0.0751
Analytical sensitivity μg/mL	0.579
Limit of detection μg/mL LOD	0.023
Limit quantification μg/mL LOQ	0.071
Enrichment Factor(EF)	11.87
Pre-concentration factor(PF)	25
Distribution coefficient(D)	320.88

Table 7. Data the accuracy and precision of the proposed method for the estimation of pure samples

Type of Medications	Amount of medications μg /mL	Relative Error %	Recovery%	Average Recovery%	RSD% (n=5)
	Taken / Found				
SFD	1 / 0.99	-1.00	99.0	100.43	0.16
	2 / 2.05	2.5	102.5		0.73
	5 / 4.99	-0.2	99.8		0.89

Table 8. The accuracy and precision of the proposed method for the estimation of commercial pharmaceuticals

Type of Medications	Amount of medications mg		Relative Error %	Recovery %	Average Recovery %	RSD% (n=5)
	Taken	Found				
Sulfadoxine & Pyrimethamine tablet the USA 500 mg	500	498.7	-0.26	99.74	99.87	0.17
		499.3	-0.14	99.86		
		500.1	0.02	100.02		
Sulfadoxine & Pyrimethamine Tablets Indian 200mg	200	200.1	0.05	100.05	100.11	0.35
		201.0	0.5	100.5		
		199.6	-0.2	99.8		

The optimum reaction conditions of flow injection analysis method.

For the optimization of chemical parameters involving the concentration of reagents, sodium nitrates and sodium hydroxide concentrations, the different concentrations of HCl acids have also been used to achieve the maximum absorption by the SFD flow injection. The optimum HCl concentration was (0.6) M, as shown in figure 16. The 4-methoxyphenol concentration between (4.989×10^{-4} -7.89×10^{-3}) M µg/ mL also raises the absorbance by increasing the 4-methoxyphenol concentration up to (5.89×10^{-3} M), decreases the absorbance by increasing the concentration as shown in Fig. 17. In this reaction, sodium nitrite has an active role and contributes to the reaction's speed and completion. Determine the optimal concentration for SFD estimation in flow injection, different concentrations of $NaNO_2$ were used, as shown in Fig. 18.

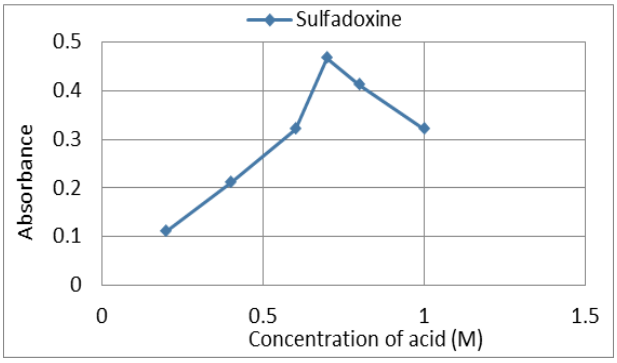

Fig.16. Effect concentration of acid

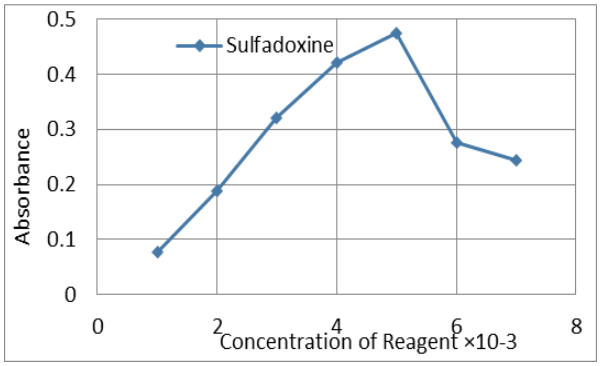

Fig. 17. Effect concentration of reagent

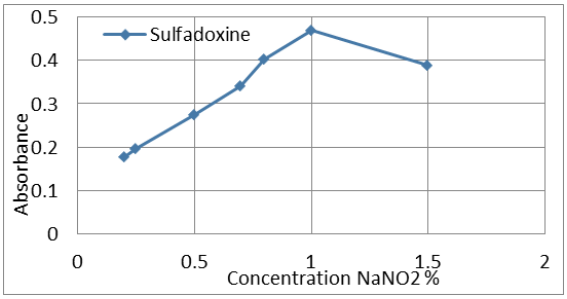

Fig.18. Effect concentration of $NaNO_2$

Study manifold optimization of parameters

Various physical parameters were studied, such as coil length, reaction coil length varying (25-230) cm, 50 cm was the best reaction coil for SFD giving high absorption at λ max 495 nm Fig.19. A total flow rate (1-5) mL/ min was, studied, with the highest absorbance produced is 2.5 mL/ min. The outcome in Fig.20 is shown by the usage fixed in all subsequent experiments. The different volume (50-200) µL of the injection sample tested, the 100 µl volume was the best volume to achieve higher absorbance and was used in all subsequent experiments, as shown in Fig.21.

Analytical characteristics

After optimization of the experimental conditions, the prepared flow injection calibration graph shows the amount of different concentrations of SFD 1-150 µg / mL against the absorbance intensity Fig.22. Table 9 displays the analytical data for the FIA process regression equation.

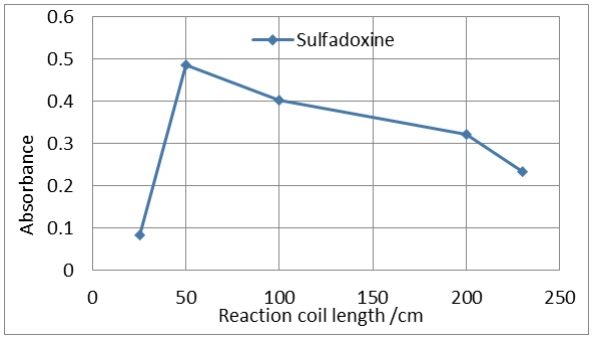

Fig.19. Effect of Length Reaction Coil /cm

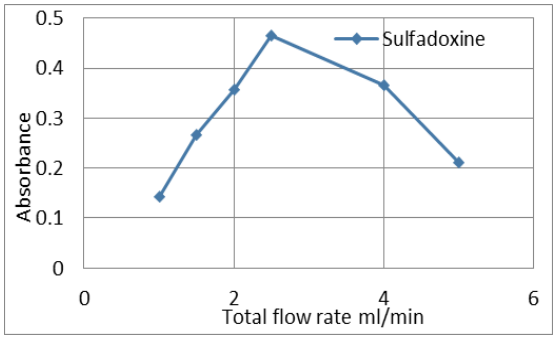

Fig.20. Effect of Total rate mL/min

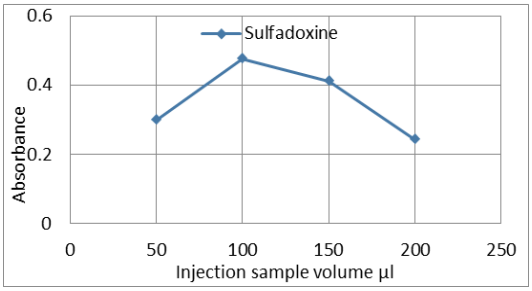

Fig.21. Effect Injection Sample Volume µL

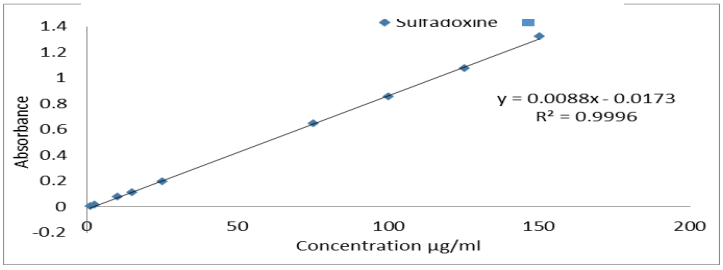

Fig.22. Calibration graph for SFD by Flow Injection Analysis

Table 9. data for the regression equation of the Flow Injection Analysis

Parameter	Sulfadoxine
λ max(nm)	495
Color	Reddish-Orange
linearity range µg/mL	1-150
Molarabsorptivity (L.mol^{-1} cm^{-1})	0.273×10^4
Sandell'ssensitivity (µg/ cm^2)	0.114
Correlation coefficient r	0.9997
Regression equation	Y=0.0088x-0.0173
Slope(b)	0.0088
Intercept(a)	-0.0173
Analytical sensitivity µg/mL	0.005
Limit of detection µg/mL	0.375
Limit quantification µg/mL	1.136

Accuracy and precision

Study the accuracy and precision of the proposed method under optimal conditions using various concentrations and the absorbance measured at a minimum of five readings per concentration. Determination of precision and precision by RE%, R% and RSD%, as shown in Table 10 and 11.

Table 10. Data the accuracy and precision of the proposed method for the estimation of pure samples

Type of Medication	Amount of medications µg /ml		Relative Error %	Recovery %	Average Recovery%	RSD% (n=5)
	Taken	Found				
SFD	5	4.970	-4.6	95.40	98.63	0.08
	10	9.99	-0.1	99.9		0.14
	15	15.10	0.6	100.6		0.19

Table 11. The accuracy and precision of the proposed method for the estimation of commercial pharmaceuticals

Type of Medications	Amount of medications mg		Relative Error %	Recovery %	Average Recovery %	RSD% (n=5)
	Taken	Found				
Sulfadoxine& Pyrimethamine tablet USA 500 mg		495.7	-0.86	99.14	99.04	1.3
		500	0.02	100.02		
		500.1	-2.04	97.96		
		489.8				
Sulfadoxine & Pyrimethamine tablets Indian 200mg		200.2	0.1	100.1	99.98	0.48
		200	0.4	100.4		
		200.8	-0.55	99.45		
		198.9				

The statistical analysis results exhibited in table 12 proved that the calculated t-values and F-values for sulfadoxine determination in different pharmaceuticals are less than t-tabulated and F-tabulated at 95% confidence interval and (n-1) degrees of freedom.

Conclusions

A simple, inexpensive, and relatively sensitive method for estimating SFD in its pure samples and pharmaceuticals was proposed in this work. The first method is based on the SFD conversion into diazotization of a colored substance. 495 nm absorbance measurement. Might point extraction method to determine the azo-dye formed trace concentration. The batch spectrophotometric approach for the estimation of the SFD drug was semi-automated using the FIA approach. The suggested methods were statistically tested and successfully applied in pure form and pharmaceutical preparation for the determination of SFD.

Acknowledgment

The authors would like to thank, Mustansiriyah University ,Baghdad , Iraq to help for complete the work, and thank to general company for the manufacture of medicines and medical supplies-Samarra) to provide pure sulfadoxine medication

Table 12. Comparison the proposed method with stander method using t and F- Statistical test at 95% confidence level

Pharmaceutical preparation	Proposed methods						Standard method[2]
	Rec% Batch method	Value t	Value F	Rec% FIA method	Value t	Value F	Rec %
Pure Sulfadoxine	98.63	0.340 (2.131)	6.26 (19.00)	98.63	1.11 (2.131)	4.87 (19.00)	99.34
Sulfadoxine & Pyrimethamine tablet USA500 mg	99.92			99.04			99.87
Sulfadoxine& Pyrimethamine tablets Indian 200mg)	100.06			99.98			99.90

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التحديد الطيفي لعقار سلفادوكسين استخدام نقطة الغيمة والحقن الجرياني في المستحضرات الصيدلانية

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الخلاصة

تم تطوير طرق طيفية حساسة جديدة وبسيطة لتقدير سلفادوكسين (SFD) في تركيباته النقية والمستحضرات الصيدلانية. تتضمن الطريقة الأولى تحويل الأمين إلى صبغة آلازو عن طريق تفاعل سلفادوكسين مع نتريت الصوديوم وحمض الهيدروكلوريك متبوعًا بالاقتران مع 4-ميثوكسيفينول في وسط قاعدي للحصول على صبغة برتقالية حمراء عند طول موجي495 نانومتر. يتراوح التركيز 0,25–60 ميكروغرام/ مل، طاع قانون بير، كان معامل الارتباط 0,9996، الامتصاصية المولارية 0,589 × 10^4 لتر مول $^{-1}$سم$^{-1}$ وكان حد الكشف 0,157 ميكروغرام/ مل. الطريقة الثانية تضمنت الاستخلاص بنقطة الغيمة (CPE) لتقدير التراكيز النزرة في محلول مائي ناتج عن صبغة الازو والقياس باستخدام مقياس طيف ضوئي مرئي للأشعة فوق البنفسجية وأعطى ناتج أرجواني محمر عند طول موجي 500 نانومتر. وطاع قانون بير عند التركيز 0,25–6 ميكروغرام/ مل، معامل الارتباط 0.9998، والامتصاصية المولارية 0.877 × 10^5لتر مول $^{-1}$ سم $^{-1}$، حد الكشف 0,023 ميكروغرام/ مل، معامل التركيز 25 ومعامل التوزيع 320,88 الطريقة الأخيرة تحليل بالحقن الجرياني، وهي طريقة بسيطة لتقدير السلفادوكسين. طاعت قانون بير عند التركيز من 1 إلى 150 ميكروغرام/ مل، معامل الارتباط 0,9997، والامتصاصية المولارية 0,273 × 10^4 لتر مول$^{-1}$ سم$^{-1}$ وحد الكشف 0,375 ميكروغرام/ مل. كانت الطرق المقدمة ناجحة ومفيدة لتقدير السلفادوكسين في الأدوية الصيدلانية.