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A New Green Approach of CFIA Technique for Direct Assay with a High Throughput of Sulfamethoxazole Drugs Using Condensation Reaction with NQS Agent

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Abstract

A new design of manifold flow injection (FI) coupling with a merging zone technique was studied for sulfamethoxazole determination spectrophotometrically. The semiautomated FI method has many advantages such as being fast, simple, highly accurate, economical with high throughput . The suggested method based on the production of the orange- colored compound of SMZ with (NQS)1,2-Naphthoquinone-4-Sulphonic acid Sodium salt in alkaline media NaOH at λ_{max} 496nm.The linearity range of sulfamethoxazole was 3-100 µg. mL^{-1}, with (LOD) was 0.593 µg. mL^{-1} and the RSD% is about 1.25 and the recovery is 100.73%. All various physical and chemical parameters that have an effect on the stability and development of the colored product were accurately studied and the designed systems have been completely implemented successfully for sulfamethoxazole quantity estimation in pharmaceutical formulations and biological samples.

Keywords: Biological samples, Green chemistry, NQS, Pharmaceutics, Sulfamethoxazole.

Introduction

Sulfamethoxazole (SMZ), chemically name is 4-Amino-N-(5-methyl-3-isoxazolyl)-benzene sulfonamide,is an antibacterial drug that is yellowish white and white colored, crystallized powder with closed molecular formula $C_{10}H_{11}N_3O_3S$ and molecular weight 253.279 g.mol^{-1}, the chemical from of the drug is illustrated in Fig.1. Mixture of sulfamethoxazole and trimethoprim which is known as co-trimoxazole[1-3] is used to treat a wide variety of bacterial infections e.g.: middle ear infections, genito-urinary tract infections, respiratory-tract infections such as bronchitis, and enteric infections. SMZ is uses in toxoplasmosis, carinii pneumonia and nocardiosis Pneumocystis. Skin reactions and gastrointestinal disturbances (vomiting and mainly nausea) are the most common adverse effects for this drug combination. Several methods have been described for SMZ drug estimation like flow injection analysis[4]. selective electroed[5], spectrophotometric method[6-8], HPLC[9-11] Electrochemical[12], and fluorometry [13] in this manuscript, an accurate, sensitive, and simple of semiautomated flow injection analysis CFIA/MZ technique[14- 18] were used to examine the quantitate

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determination of sulfamethoxazole in pharmaceutical samples and medical preparation.

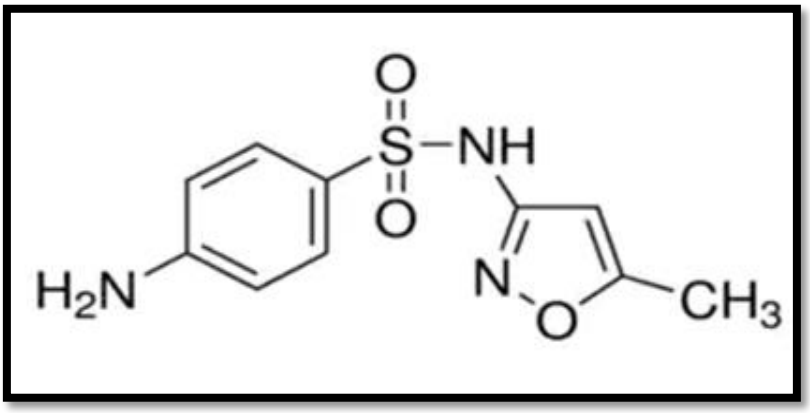

Figure 1. Chemical composition of SMZ.

Materials and Methods

The State Company for Medical Appliances and Drug Industries Samara, Iraq, presented the highest purity (99.99%) sulfamethoxazole powder as a gift (SDI). All of the chemicals and agents used are of analytical grade.

Preparation of Stock SMZ Solution (M.wt 253.279 $g.mol^{-1}$ SDI): (1000 $\mu g.mL^{-1}$) weighed 0.1 g natural substance of SMZ, d was issolved in 5mL methanol and the volume was made up to the mark in 100 m L distilled water volumetric flask.

NQS (1,2-Naphthoquinone-4-Sulphonic Acid Sodium Salt) M.wt = 260.20 $g.mol^{-1}$, Merck) (2.70×10^{-2} M): solution 0.7% (m/v) in D.W. was prepared daily.

NaOH Sodium Hydroxide [1M] (M.wt 40 $g.mol^{-1}$ BDH)**:** was prepared by dissolving 4g of NaOH in distilled water and the volume was made up to the mark in 100 m L volumetric flask.

Preparations of SMZ Pharmaceutical (1000 µg. mL^{-1})

The proposed approach examined the trading sources four pharmaceutical formulation obtained from various companies and available for injection the use of an injection valve to supply:

1. Septrin, tablet, Aspen Germany 400

2. Gdoprim, tablet, India 800

3. Supreme, tablet, India 160

4. Methoprim tablet Samara, Iraq 400

Furthermore, dilute solutions were prepared with the concentration within the calibration curve. A recovery experiment was performed by applying the standard-addition technique.

Preparation of Serum Samples

A healthy volunteer provided the sample, which was then gently thawed and kept at a temperature of around 20 °C until it was needed. 100 $\mu g.mL^{-1}$ of serum was used to prepare the sample, and it was tested for precision and accuracy and analyzed thrice [22].10 $\mu g.mL^{-1}$ SMZ of spiked solutions of biological samples was prepared by transferring 1 mL of biological samples to a standard volumetric flask 10 mL followed by addition 1 mL of SMZ, solutions were tested for accuracy and precision .

Preparation of Interferences

Dissolving 0.1 g from any one of the interferences such as sucrose, cellulose, lactose, glucose, and sodium citrate in 100 mL of distilled water by using a 100 mL standard volumetric flask.

Apparatus and FIA Manifold

The spectrophotometer with flow cell made of (quartz silica, 1cm) with (an internal volume of 80 µL) is inside the detection unit and, 1cm an optical route period is used for the absorbance including common top expressed in mV (n=3) at the optimum

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VIS 9200.The CFIA/MZ one-channel manifold is in use for spectrophotometer SMZ estimation. The peristaltic pump (Master flexC/L, channel, USA) with power supply (Yaxun, 1501 AD, China) was used to pump D.W as carrier stream and solutions by passing it into the injection valve (homemade) six-3-way injection valve with 3 loops. Chemical compounds and reference solutions are primarily based on MZ version. The injection valve was utilized to supply amounts of sample and reagent solution. Flexible vinyl tubes with a radius of 0.22 mm were used for the peristaltic pump; the reaction coil is made of glass material with a diameter of 2 mm (I.D). Fig. 2 depicts every component of the CIFA with details SMZ, NaOH, and NQS were loaded combined with carrier stream (distilled water). After that, everything was combined in a mixing coil with a length of 50 cm and a carrier flow rate of 9.2mL/min. The highest absorption was measured at 496 nm for orange-colored product.

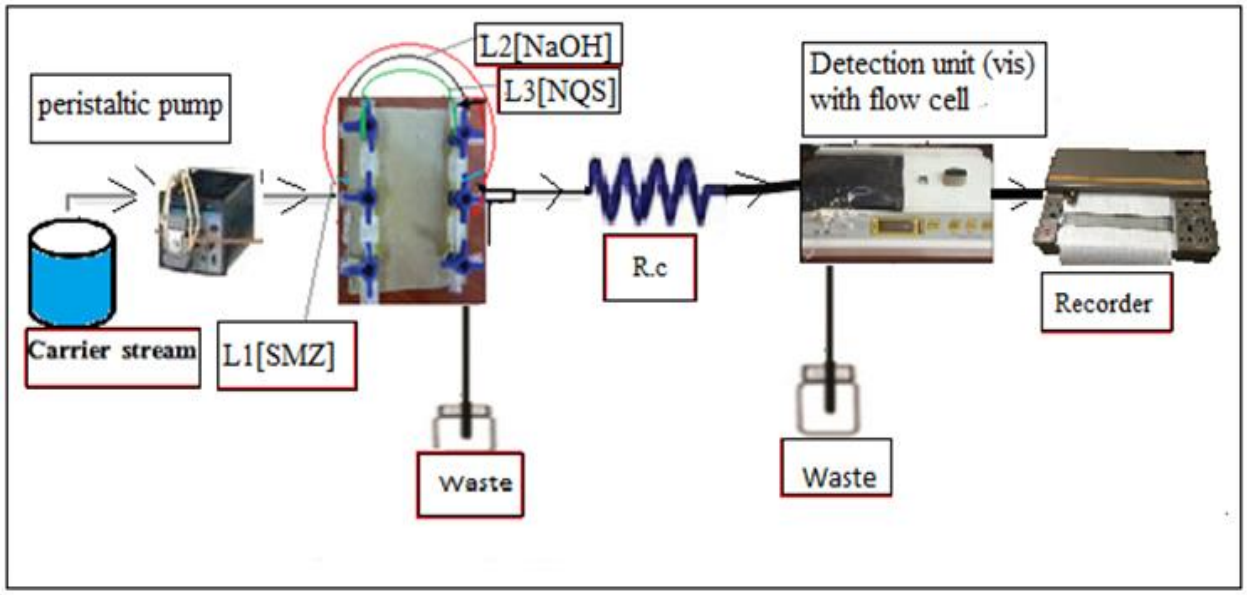

Figure 2. The developed CFIA system.

Results and Discussion

Batch Method

Different aliquants 0.5-40 µg.mL^{-1} of the sulfamethoxazole drug 1000 µg.mL^{-1} were prepared into 10 mL flask. 1 mL of 1 M, NaOH solution was added to all flasks, then 1.0 mL of 0.7 % (m/v) NQS solution was added. The solutions were completed with distilled water to the mark in a volumetric flask of 100 mL, the colored product was dark orange at 496 nm opposite reagent[19].

The Absorption Spectrum and Reaction Pathway

The solution 10 µg.mL^{-1} of sulfamethoxazole was mixed with 1 mL of 0.7 % NQS NQS in the presence of 1ml of 1M NaOH to form N-alkylamono naphthoquinone by replacing the sulphonate group of the naphthoquinone sulphonic acid by an amino group. The colored product orange appeared at wavelength 496 nm opposite blank as shown in Fig.3.thus the suggested mechanism below is likely to be as shown in Scheme 1.

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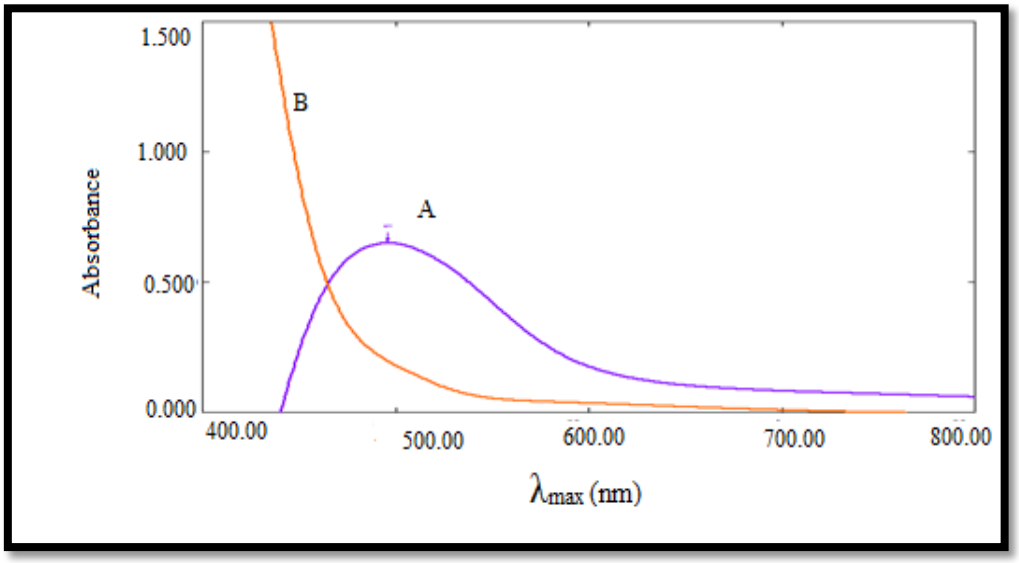
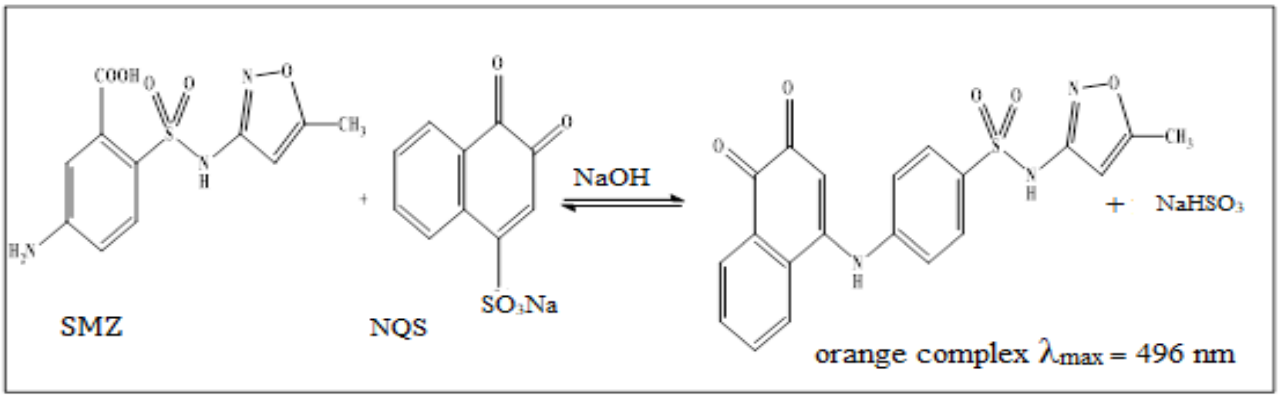


Figure 3. Absorption spectra for A/ SMZ (10µg.mL^{-1}) with NQS in basic medium against the B/blank solution.



Scheme 1. The suggested mechanism of the complex between SMZ and NQS.

The proposed mechanism for SMZ drug reacted with NQS in alkaline media to produce orange-colored product according to condensation reaction, where the drug SMZ has an amino group, it involved in yielding colored produced by nucleophillic displacement of the sulfonic acid group of NQS in alkaline medium.

Optimize the Conditions for the Estimation Process

The optimum effect of NQS estimated by adding 1 ml from various volume (0.25-2.5) of NQS, it was found that 1 ml of a 0.7% NQS solution gave the highest absorbance value, Fig.4-A shows the effect of NQS volume and the volume of NaOH was examined the best volume was 1 ml of 1M NaOH . The absorption rate reached a maximum as shown in Fig.4-B.

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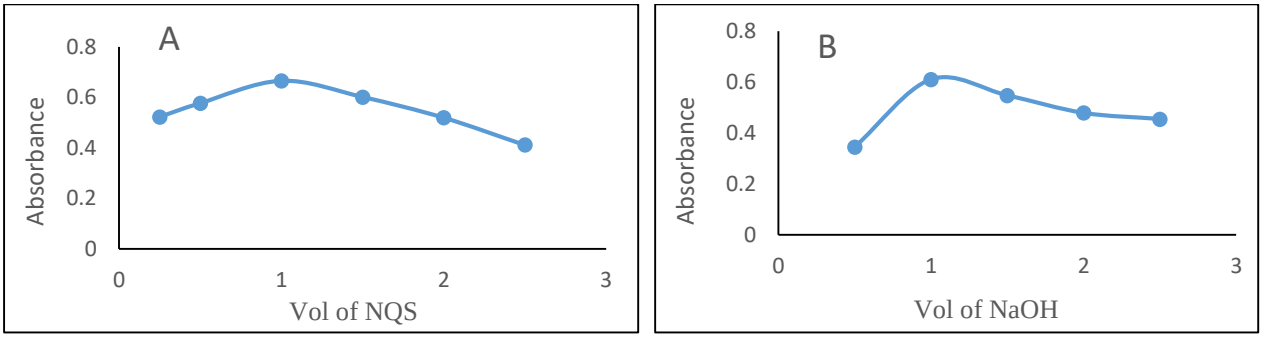

Figure 4. Chemical parameter for batch A/ volume of NQS, B/volume of (NaOH).

Calibration Graph for the Estimation of the Drug:

The suggested method showed the effect of drug concentrations on absorption behavior at optimum conditions .The results are shown in Fig.5. The linear range of 0.5-40 µg.mL^{-1} for the SMZ drug. Table 1 shows that the approach method has the best accuracy and precision.

Table 1. Accuracy and precision.

SMZ µg.mL^{-1}		Error	Rec%	Erel%	RSD%
Present µ	Found $\bar{x}$				
10	10.39	0.3900	103.90	1.200	0.608
20	19.76	-0.2400	98.80	-0.800	1.833
		$\bar{x}$	101.350	0.200	1.221

***Average of five determination**

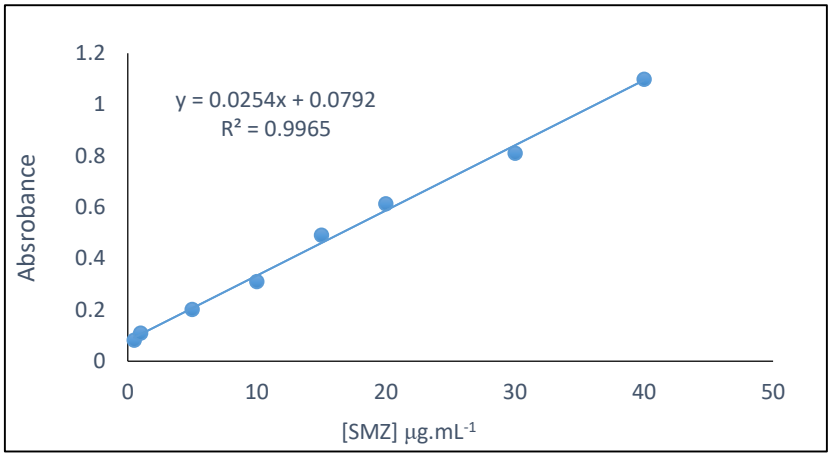

Figure 5. Liner range for estimation of SMZ drug using the batch method.

Stoichiometry Study

For the spectrophotometric determination of the colored product the stoichiometry was to calculate the ratio between the drug and reagent using obs and the mole ratio methods[20]. The results obtained as in Fig.6, gave a value maximum at Jobs and mole ratio methods (a, b) respectively, 1:1 ratio was for drug and reagent.

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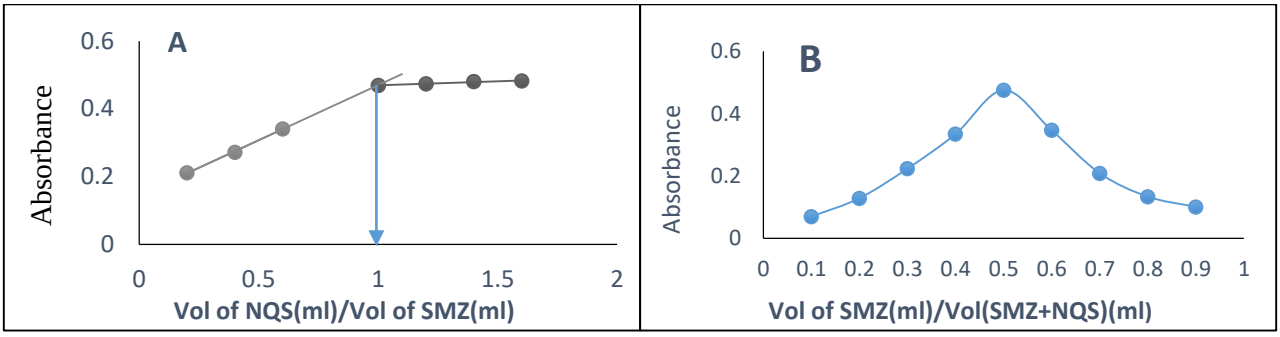

Figure 6. The stoichiometry between SMZ with NQS, A\ mole ratio B\ job's method.

Calculations of Stability Constant

The observed stability constant for the proposed interaction (SMZ: NQS) was found by relationship:

D + R ⇄ DR $K = \frac{[DR]}{[D][R]}$ $K = \frac{(1-\alpha)}{\alpha C}$ $\alpha = \frac{AM-AS}{AM}$

αC αC (1-α)C

K is the stability constant, C is the product's molar concentration (M), and (α) is the degree of dissociation. Where

Am; As are the absorbance values of the aqueous solution, which contains a sufficient and stoichiometric quantity of the reagent. The spontaneous of complex formation reaction (ΔG value) was estimated based on K evaluation as in Table 2 and the equation: ΔG = -RT lnK

Table 2. The parameters for evaluation of complex stability constant.

	Am	As	α	K ($Lmol^{-1}$)	ΔG ($J.mol^{-1}$)
1	0.476	0.469	0.01470	7801	-102123
2	0.479	0.473	0.01252	1485	-103719
Average				1138	-102921

Flow Injection/ Merging Zones Spectrophotometric Determination

The initial studies batch method and choosing the optimum conditions of reaction of SMZ with NQS in presence of NaOH utilizing the flow injection-merging zones method, the spectrophotometric reaction was automated for the purpose of the suggested study methodology.

The Manifold of FIA System

With completing the installation of the system and its connected components, the investigation of the best design choice of a homemade FIA system began. Figure 2 shows the created system, which consists of one line that delivers distilled water to the injection valve and 3 loops (various loop lengths with 0.5mm I.D.) fill with drug, basic medium, and reagent as follow SMZ in L1, NaOH in L2, and NQS in L3.

Optimization of the Developed FIA Chemical Variable

The best basic medium was found, which is NaOH for reaction between drug with reagent, other medium such as, NH_4OH, KOH, and Na_2Co_3 were examined, the NaOH is the best base type which is shown in Fig.7-A, B. by utilizing different concentration of sodium hydroxide solution ranged from 0.05 to 0.25 M the concentration (0.1M) gave the best response and good repeatability, optimum concentration of NQS as a reagent was examined by using several concentrations (2×10^{-3} - 7×10^{-3} M) utilizing handmade seven-three-way injection valve. The results in Fig.7-C that (6×10^{-3}) M of NQS was highest value of absorbance. The results in Fig.7-D appear to be optimum sequence is (D in L1 + B in L2 + R in L3) where D is SMZ, B is NaOH and R is NQS.

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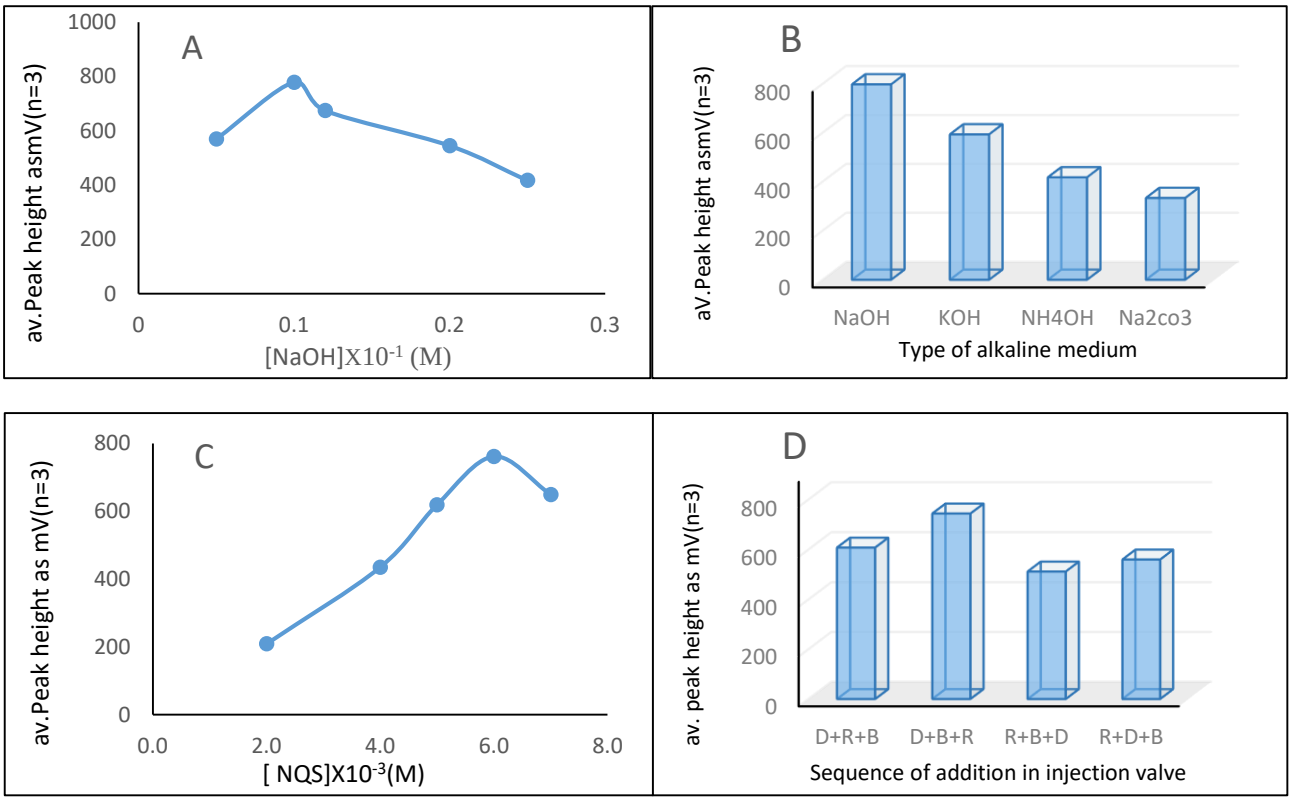
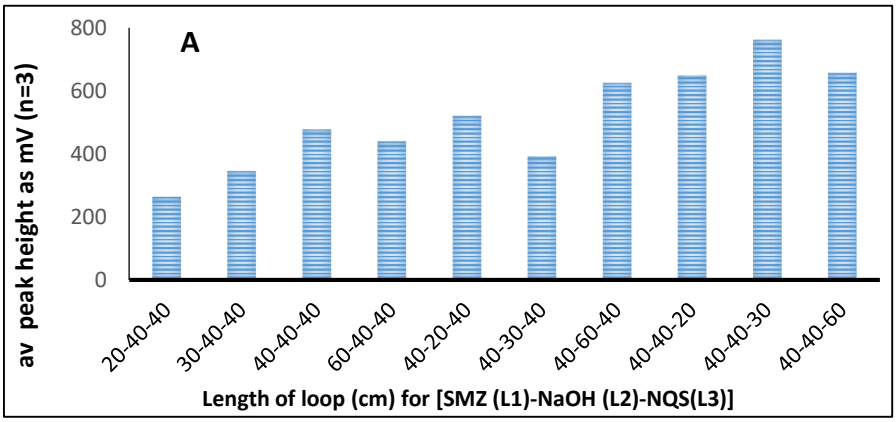


Figure 7. Chemicals parameter A\ NaOH concentration, B\ Type of NaOH, C\ NQS concentration, D\ sequence of reaction.

Physical Variables

For [SMZ, NaOH, NQS] CFIA system the best loop volume for drug, basic medium, and reagent were (78.5-78.5-58.88) µL shown in Fig.8-A in addition to the better reaction coil length was (50 cm) as shown in Fig.8-B. All available flow rates were studied for the developed FIA system, a flow rate was 10 ml/min with sample through-put of about 85 samples. hour^{-1} as shown in Fig.8-C. The sampling rate was calculated based on the time it took to put the solutions into the seven three-way valve loops 15 sec, plus the time required to maximum peak height appear 27 sec so the sampling rate was 85 samples. hour^{-1}.



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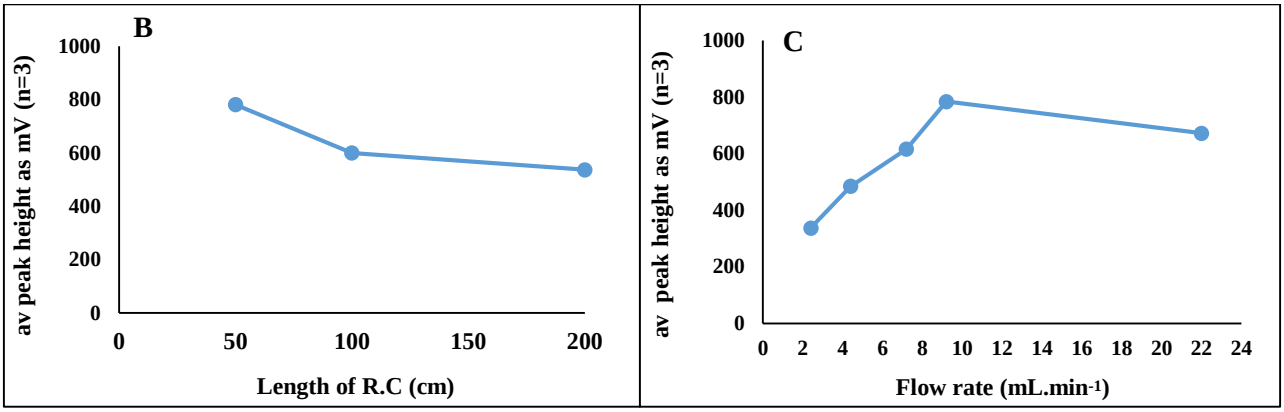

Figure 8. Physical parameter A\ Injected volume, B\ Reaction coil, C \ Total flow rate.

Purge Time

Utilizing the most beneficial physical and chemical parameters that had previously been examined while analyzing sources for acquired pharmaceutical, the purge time for the sample that would be placed into the carrier stream (distilled water) was established. The maximal reaction intensity occurred when the purge time exceeded 20 seconds for time intervals of 5, 10, 15, and 20 seconds along with an open valve. This case is shown in Fig. 9. The open valve for full sample transport from the sample loop to the flow cell was the best purge time.

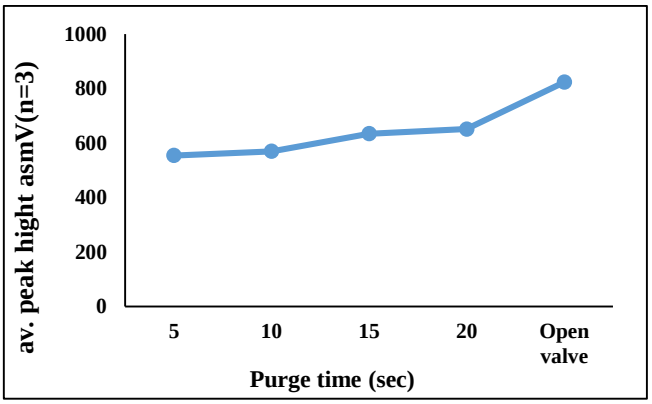

Figure 9. Effect of purge time.

Estimation of Dispersion

Dispersion is one of the physical phenomenons important in the FIA method, it is definition as the ratio of the different concentration solutions expressed by: $D = C_o / C_{max}$, the mean (D) coefficient of dispersion, all of the chemical were combined in flask, and the solution was passed through the FIA system carrier stream (distilled water) to get constant value expressed by (C_o). In the second beaker, SMZ in L1, NaOH in L2 and NQS in L3. using distilled water in system as a carrier and the component injected works to push the components to the reaction coil and then to the detector, responses appeared represented by (C). C_{max}: peak height with dilution inside the FIA system C_o: peak height without dilution outside the FIA system dispersion drug values were1.378, 1.258 for the 2 concentrations 10 and 50 µg.mL^{-1} of SMZ respectively as shown in Fig.10.and Table. 3.

Table 3. Dispersion value of SMZ.

[SMZ] µg.mL^{-1}	C_o (cm)	C (cm)	D
10	5.1	3.7	1.378
50	11.2	8.9	1.258

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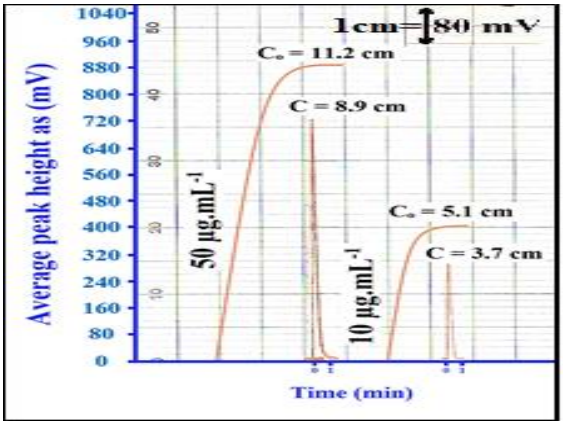

Figure 10. Dispersion of SMZ in CFIA system.

Calibration curve in FIA Method

A several series of SMZ concentrations were prepared from the standard solution with the use of NQS reagent and NaOH and inject into flow injection system the best range of concentration was 3 -100 µg/mL as shown in Table. 4 and Fig.11.

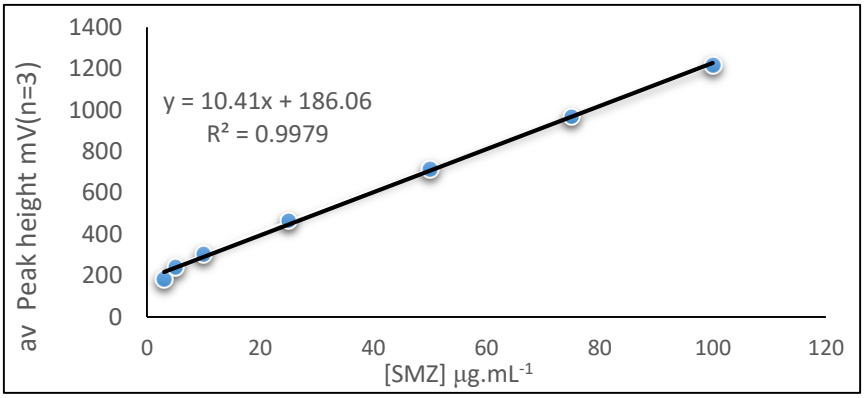

Figure 11. Linear dynamic range for estimation of SMZ

Table 4. Product–moment relationship between absorbance (mv)various concentrations for [SMZ-NQS-NaOH] CFIA system.

[SMZ] µg.mL^{-1}	peak height (mV)			Average response ($\bar{y}$) (mV)	*RSD%	S.E.M	*E/y%
3	182	182	183.2	183	0.25	183 ± 1.147	0.63
5	240	241	240	240	0.19	240 ±1.147	0.48
10	304	302	304	303	0.31	303 ±2.353	0.78
25	465	463	465.6	465	0.26	465 ±3.034	0.65
50	714	720	713.6	716	0.49	716 ±8.657	1.21
75	961	968	976	968	0.79	968 ±18.88	1.95
100	1214	1218	1215.2	1216	0.14	1216±4.134	0.34

* $Ey\% = ttabSD/\sqrt{n} \times 100\% y$, S.E.M=$\bar{y}$ ± t0.05 ($\sigma n - 1\sqrt{n}$)

Analysis of Variation and Repeatability

For (n2) degrees of freedom, (imply mistake), and call (about regression), calculate the sum of squares of the variance between the values of yi (response) and I (appraiser response) . The sum of squares of the difference of the values yi (due to regression) from the mean value was calculated to get the total of squares (S1)2, then the result was divided by the number of degrees of freedom (So)2 to get the result (F), as shown in Table. 5. F_{crit} 4.74722 << F 15.2957. As a result, it is feasible to draw the conclusion that the SMZ concentrations and the signal received are directly related. The technique had good reproducibility as shown in Table 6.

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Table 5. Analysis of variation for developed FIA method

Source of Variation	Sum. Of Squares SS	df	Mean of Squares MS	F (S_1^2/S_2^2)	F crit
Between Groups	1196208.5	1	1196209	15.29567	4.74722
Within Groups	938467.88	12	78205.66		
Total	2134676.4	13			

Table 6. Repeatability of consecutive measurement of SMZ(n=6).

[SMZ] µg.mL^{-1}	Found	Error	*Rec%	*Erel%	*RSD%
25	25.201	0.201	100.804	0.804	1.226
50	50.332	0.332	100.664	0.664	1.283

***Average of six determination**

Method Validation

The linearity with this approach was estimated depending on using ideal conditions, the analytical characteristics of each technique, such as the correlation coefficient (r), linear range, detection limit (LOD), (LOQ) [21,22] and RSD were calculated as shown in Table 7. For a series of standard solutions (SMZ) and the fundamental analytical figure of deserts proposed by the approach, a liner calibration curve was constructed, Fig.11: slope (Sb); intercept (Sa); and standard deviation for residuals (Sy/x) within 95 percent confidence limits for (n-2) degrees of freedom was given in a statistical analysis of the regression line. When comparing the suggested CFIA technique with the classical method, the best repeatability with high reproducibility of the data appeared. The CFIA technique was simpler and easier since it was quick to analyze (sample throughput of 85 samples per hour); the calibration curves were created with a large linear scale.

Table 7. Analytical characteristic of calibration curve for the reaction SMZ with NQS and NaOH.

Parameters	FIA method	Batch method
λmax (nm)	496	496
Regression equation	y=10.41x+186.06	y=0.0254x+0.0792
Linear range (µg mL^{-1})	3 -100	0.5 -40
Average of recovery (%)	100.73	101.35
Average of Relative Error %	0.73	1.35
(RSD %)	1.25	1.036
Slope (b)	10.41	0.02
Intercept (a)	185.84	0.02
Linearity R^2	0.9979	0.9965
R^2%	99.79	99.65
Correlation coefficient (r)	0.9989	0.9993
Standard deviation of slope (Sb)	0.210	0.006
Standard deviation of intercept (Sa)	10.920	0.013
Limit of detection	1.184	0.789
Limit of quantification	3.949	2.632
Molar absorptivity Ɛ (L/mol.cm)	----	5141.564
Sandell s sensitivity (S)	----	0.049
Sample through put (h^{-1})	85	
Standard deviation of the residuals	19.5252	0.0186
Confidence limit of slope (b)	10.40 ± 0.5151	----
Confidence limit of intercept (a)	186.06 ± 26.7559	----

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Effect of Interferences

The suggested method's selectivity was evaluated, and the influence of many typical excipients such as (starch, sodium citrate, cellulose, glucose, lactose, and sucrose) was studied, which often accompany drugs, were examined by estimating of SMZ 100 $\mu g.mL^{-1}$ in the presence of the above excipients. The results in Table. 8, indicate no interferences were found from any of the excipients studied in the estimation of SMZ utilizing the new CFIA system, as shown in Table 8.

Table 8. Interferences effect on[SMZ-NaOH-NQS].

Type of Interference	conc.of Interferences $\mu g.mL^{-1}$	Average Response ($\bar{y}$) (mV)	*Erel%	*Rec%
Standard		292	1.5626	101.56
	5	293	2.7922	102.79
Sucrose	10	292	1.9212	101.92
	25	290	-0.2818	99.72
cellulose	5	290	-0.5379	99.46
	10	295	4.8159	104.82
	25	294	3.2097	103.21
lactose	5	289	-1.3858	98.61
	10	294	3.3301	103.33
	25	288	-2.4592	97.54
glucose	5	289	-1.5626	98.44
	10	289	16.0871	116.09
	25	289	-1.2552	98.74
Sodium citrate	5	290	0.0256	100.03
	10	293	2.3055	102.31
	25	291	0.3842	100.38

*** Average of five determinations.**

Applications and Assessment of the Suggested Method

Several types of pharmaceutical products containing SMZ that have unique origins and use the conventional addition process were examined using the suggested methodology in this study using statistical analysis using the student F-test and t-test .It was demonstrated that the calculated F-test values-3.3876 with 2.2072, T-test values-1.5494 and, 0.957-were less than the theoretical F-test values-9.28 and t-test-2.45 by using CFIA/MZ. The findings of the recommended technique were compared with method HPLC the estimation of SMZ in a sample of spiked human serum is also accomplished satisfactorily using the FIA method. 100 $\mu g\ mL^{-1}$ of SMZ underwent testing to determine its precision and accuracy. We looked at each concentration three times. The serum samples showed satisfactory repeatability, as shown in Table 10.

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Table 9. The proposed method application was compared to the official method for determining SMZ in pharmaceutical formulations.

Dosage form	Classical method					Official method				
	Conc of SMZ µg.mL^{-1}		Erel %	Rec %	RSD %	Conc of SMZ µg.mL^{-1}		Erel %	Rec %	RSD %
	Present	Found				Present	Found			
Septrin,tablet, spen Germany 400	10	10.19	1.90	101.90	1.16	10	9.89	1.10	98.90	2.14
	50	50.10	0.20		0.25	50	50.23		100.46	0.32
Gdoprim, tablet, India 800	10	10.10	1.00	100.20	1.18	10	9.61	0.46	96.10	2.20
	50	49.9	-0.20	101.00	0.21	50	50.11	3.90	100.22	0.32
Supreme, tablat.India 160	10	9.91	-0.90	99.80	1.20	10	10.02	-0.22	100.20	2.11
	50	50.20	0.40	99.10	0.25	50	49.92			0.33
Methoprim,tablat,Samara,Iraq 800	10	10.11	1.10	100.40	1.17	10	10.09	-0.20	99.84	2.10
	50	50.09	0.18	101.10	0.26	50	49.89	100.90		0.32
				100.18				0.16	99.78	
								-0.90		
								0.22		

$t\,tab$=2.45 $for\ n1$=$n2$=4,$n1$+$n2$−2=6,at 95% $confidence\ level\ Ftab$=9.28 $for\ n1$−1=$n2$−1=3,at 95% $confidence\ level$

Table 10. Determination of SMZ in serum samples using the suggest CFIA system.

Samples	SMZ µg.mL^{-1} Present(µ)	Found($\bar{x}$) µg.mL^{-1}	Erel%	Rec%	RSD%
1	10	9.98	-0.1537	99.85	0.33
2	10	9.79	-2.0749	97.93	1.44
3	10	10.08	0.8069	100.81	1.27
4	10	10.27	2.7281	102.73	1.61
5	10	10.18	1.7675	101.77	1.95
6	10	9.89	-1.1143	98.89	2.32
7	10	10.37	3.6888	103.69	2.62

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Conclusion

After the survey and investigation of research in the system of CFIA, it was found that no research has been published so far dealing with the estimation of SMZ drug in pure material and biological samples. Therefore, the distinctive and new research idea was to estimate the drug spectrophotometrically using CFIA system. The key advantages of CFIA techniques include their broad working range, reasonable sensitivity, and applicability for routine assessment in pharmaceutical quality control laboratories .By comparing the proposed method and the batch method, it was found that it consumes less amount of organic reagents.

Authors' Declaration

- Conflicts of Interest: None.
- We hereby confirm that all the Figures and Tables in the manuscript are ours. Furthermore, any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- The author has signed an animal welfare statement.
- Authors sign on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee in University of Baghdad.

Authors' Contribution Statement

W. A. H. prepared the samples, carried out the data collection, interpretation, analysis the data, and revision. B .B. Q. did the study's design and editing.

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طريقة خضراء جديدة لتقنية التحليل الحقن الجرياني المستمر للتقدير المباشر مع نمذجة عالية للمجموعة الفعالة في السفوناميد في ادوية السلفاميثوكسازول باستخدام تفاعل التكثيف مع كاشف 2,1- نفثوكوينون-4- حامض سلفونيك

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الخلاصة

تمت دراسة التصميم الجديد لمنظومة الحقن الجرياني المتشعب المقترنة مع تقنية اندماج المناطق المتلاقية لتحديد سلفاميثاكسازول بطريقة طيفية تتميز طريقةالحقن الجرياني الشبه المؤتمت باالعديد من المزايا مثل السرعة , البساطة, الدقة العالية ,اقتصادية مع نمذجة عالية. الطريقة المقترحة تعتمد على تكوين مركب برتقالي داكن الون مع كاشف كاشف 2,1- نفثوكوينون-4- حامض سلفونيك في الوسط القاعدي من هيدروكسيد الصوديوم عند طول موجي 496 نانومتر كانت مديات الخطية للسلفاميثوكسازول 3-100 مايكروغرام .مل$^{-1}$ مع حدود كشف 0.593 مايكروغرام.مل$^{-1}$والانحراف المعياري النسبي حوالي 1.25 وكانت النسبة المئوية للأسترداد ٪100.73 تم دراسة جميع الظروف الفيزيائية والكيميائية بدقة التي لها تأثير على استقرارية الناتج الملون , تم تنفيذ الانظمة المصممة بالكامل لتقدير كمية السلفا في المستحضرات الصيدلانية والعينات البايولوجية.

الكلمات المفتاحية: النماذج البايولوجية ،الكيمياء الخضراء ، سلفاميثوكسازول، مستحضرات الصيدلانية،1,2-نفثاكوينون-4-حامض السلفونيك.