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New Green Modalities of Flow Injection Technology for Assaying Anti-Allergic Drugs in Pharmaceutics and Biological Samples

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Abstract

A new approach and the developed FIA technique with many advantages (economic, fast, simple, accurate, and high throughput) are used to determine the decongestant drugs (Phenylephrine.HCl, Oxymetazoline.HCl) in biological samples, pharmaceutical formulations, and pure samples via continuous flow injection technique by oxidative coupling reaction, where the method depends on the interaction of the decongestant drug with organic reagents to produce colored compounds, where Phenylephrine reacts with 4-AAP at λ_{max}503 nm to produce a red compound, and the Beer's law range of 10-600 $\mu g.mL^{-1}$. As for Oxymetazoline, it reacts with DNPH at λ_{max} 631nm to produce a green compound with a linear dynamic range of 5-400 µg/mL. The limits of detection were 9.24 and 4.67 $\mu g.mL^{-1}$, respectively. The veracity of recovery (%) was 100.24, 100.68, RSD% were 3.44, 2.51 and sampling was 60,77 $sample.h^{-1}$ for PHE and OXY successively. Distilled water was used as a carrier to transport chemicals within the minute ports of the new system. Statistical data treatment using analysis of variance one-way ANOVA was used for the determination of drugs in dosage forms, and the results obtained were compared with the official method (AOAC) and British pharmacopeia.

Keyword: PHE.HCl, KIO_4, OXY.HCl, 4-AAP, CFIA technique, DNPH, biological samples.

1. Introduction

Phenylephrine and Oxymetazoline hydrochloride are white crystalline powders that belong to the anti-allergic drugs and act directly as agonists at the adrenergic receptor [1]. It is administered orally as drops or a spray for the nose and used topically as a decongestant in a variety of conditions, such as benign nasal tumors, allergies, colds, flu, and sinusitis [2, 3]. There are various methods in the literature for analyzing Phenylephrine.HCl, including spectrophotometry [4,5], spectrophotometry with chromogenic reagent [6], chromatography [7], HPLC [8–10], micellar

liquid chromatography [11, 12], and capillary zone electrophoresis [13]. And there are different methods for determining OXY in pharmaceutical preparations and biological samples; they include HPLC [14, 15], Spectrophotometric [16], LC-MS [17], FI/CL [18], Fluorophotometric [19], and potentiometry [20].

The flow injection analysis (FIA) technique has been suggested for its high throughput sample per hour performance in a short analysis time, affordability, user-friendliness, green chemistry, accuracy, and remarkable reproducibility of the results found. It does not need to treat the samples further or use an expensive or toxic reagent. Several samples can have anti-allergic identified using low-cost, automated, and user-friendly analytical procedures. Based on an oxidative coupling reaction or other reaction with an organic reagent [21.22], The proposed CFIA/MZ technique for determining PHE and OXY in pure pharmaceutical formulations and biological samples is described in this manuscript. The colored product is measured at a maximum wavelength of 503 and 631 nm for PHE and OXY, respectively.

Experimental

Material and reagents

- Weighing 0.1g of the pure ingredient and adding distilled water to the mark in a 100mL volumetric flask produced the stock solution of the drugs PHE and OXY (1000 μg. mL^{-1}, M.wt. =203.66, 296.83 $g.mol^{-1}$, respectively, SDI).
- The reagent's stock solution, 4-aminoantipyrine (4-AAP) (4.9×10^{-2} M, M. wt=203.24 $g.mol^{-1}$) was prepared by dissolving 0.995gm of the compound in a100 mL volumetric flask with D.W. And a stock solution of DNPH (1×10^{-2} M, M. wt=198.14 $g.mol^{-1}$) was prepared by dissolving 0.198 gm in 5mL of concentration sulfuric acid, then completing it to 100 mL with distilled water in volumetric flask.
- Oxidizing agent: In these two reactions, the same oxidizing agent is used (potassium periodate) as for the PHE reaction, a stock solution of KIO_4 (6×10^{-3} M, M. wt =230 $g.mol^{-1}$) was prepared by dissolving 0.131 gm in 100 mL volumetric flask with distilled water and completing it to the mark.
- Sodium hydroxide stock solution (4M, M. wt= 40 $g.mol^{-1}$) was prepared by dissolved 16 gm with 100mL D.W in a volumetric flask.

1.1 Apparatus and FI manifold

Using a quartz cuvette with an optical longitude of 1 cm and a Shimadzu UV- 1800 UV-Visible Spectrophotometer (Japan), all absorbance in the batch operation was measured. According to the proposed FIA/merging zones system approach in this scientific manuscript [23], the suggested FI manifold was made as a straightforward type with a single canal technique, as illustrated in Figure 1. The peristaltic pump (Master Flex C/L, two channel, USA), which travels at 90° and has three Teflon loops (I.d = 0.5 mm), was used to pump the carrier stream (D.W) through the injection valve (six three-way injection valve, homemade), into which the sample (L1), reagent (L2), and oxidizing agent (L3) were loaded. The glass reaction coil is used to combine the chemicals (2 mm, I.D.). FIA processes were performed through a modified Optima photometer 301-D+ (VIS-Spectro one beam) (Japan) to measure all absorbance and spectrum measurements. Using a Kompensograph C1032 (Siemens) or a Chinese optical multimeter (DT9205A, OVA) for measuring absorbance, the responses, expressed as peak height mV (n=3), were measured.

An altered detecting unit contains a flow cell made of quartz silica (QS, 1 cm) with an internal volume of 80 µL.

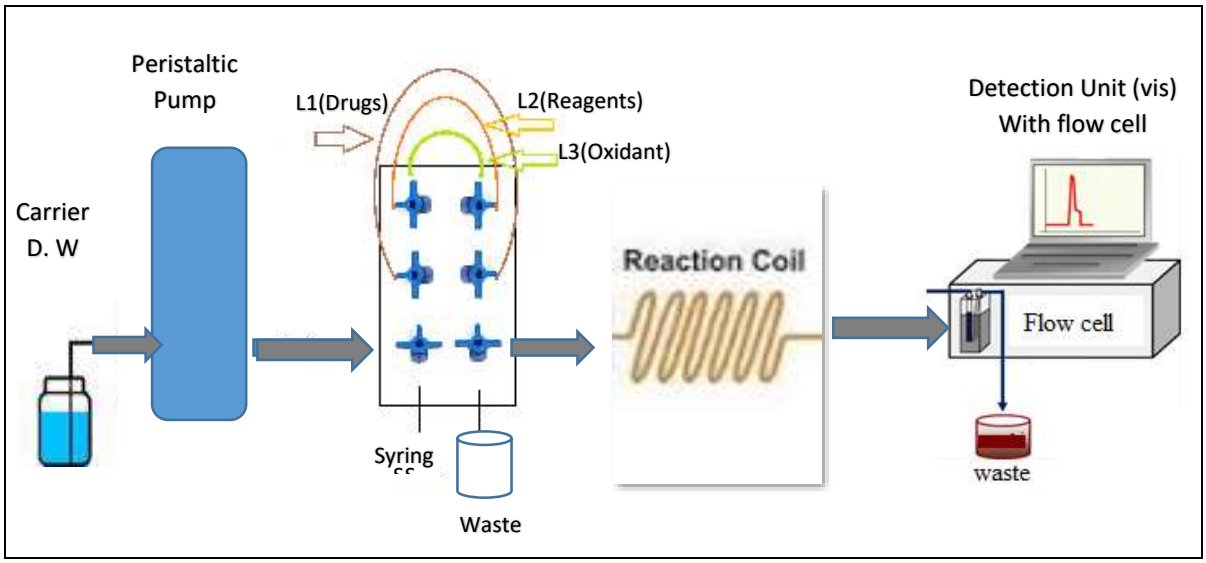


Figure 1. Diagram of FI manifold used for determination of anti-allergic in pharmaceutics and biological samples.

2.2 Preparation of pharmaceutical

Three PHE medication pharmaceutical formulations were created by various firms as syrup and drops. [Rinoraz (syrup)5 mg, Aleppo-Syria], [Nazafrine (drops)10mg, Diala- Iraq], [Nazophen (drops) 10 mg, Pioneer Co.-Iraq].

Two pharmaceutical preparations of the OXY drug were prepared in the form of drops from different companies [Oxymetazoline-MUP 0.5 mg, Egypt], and [Alerjon 0.25 mg, Portugal].

Biological specimen (plasma) preparation

Samples of PHE and OXY were obtained from healthy individuals, centrifuged for 15 minutes, and then stored in the freezer until use [24].

2.3 The suggest mechanism of two reactions and general classical procedures.

- **PHE**

Spectrophotometric determination of PHE based on coupling of 1 ml 4-AAP (4.9×10^{-2}) M with drug 1ml from (100 µg. mL^{-1}) in the presence of potassium periodate (1ml, 6×10^{-3} M) as an oxidizing agent was added in a 10ml volumetric flask to form a colored product (red), measured at λmax503 nm as seen in Figure 2-A and Scheme 1.

- **OXY**

Spectrophotometric determination of a 1ml OXY from (100 µg. mL^{-1}) based on oxidation of 1ml of DNPH (1×10^{-2}) M with 1ml of KIO_4 (1×10^{-2}) M, as an oxidizing agent in alkaline medium was added to a 10ml volumetric flask to form a color product (green), measured at λmax 631 nm as seen in Figure (2-B) and scheme 2.

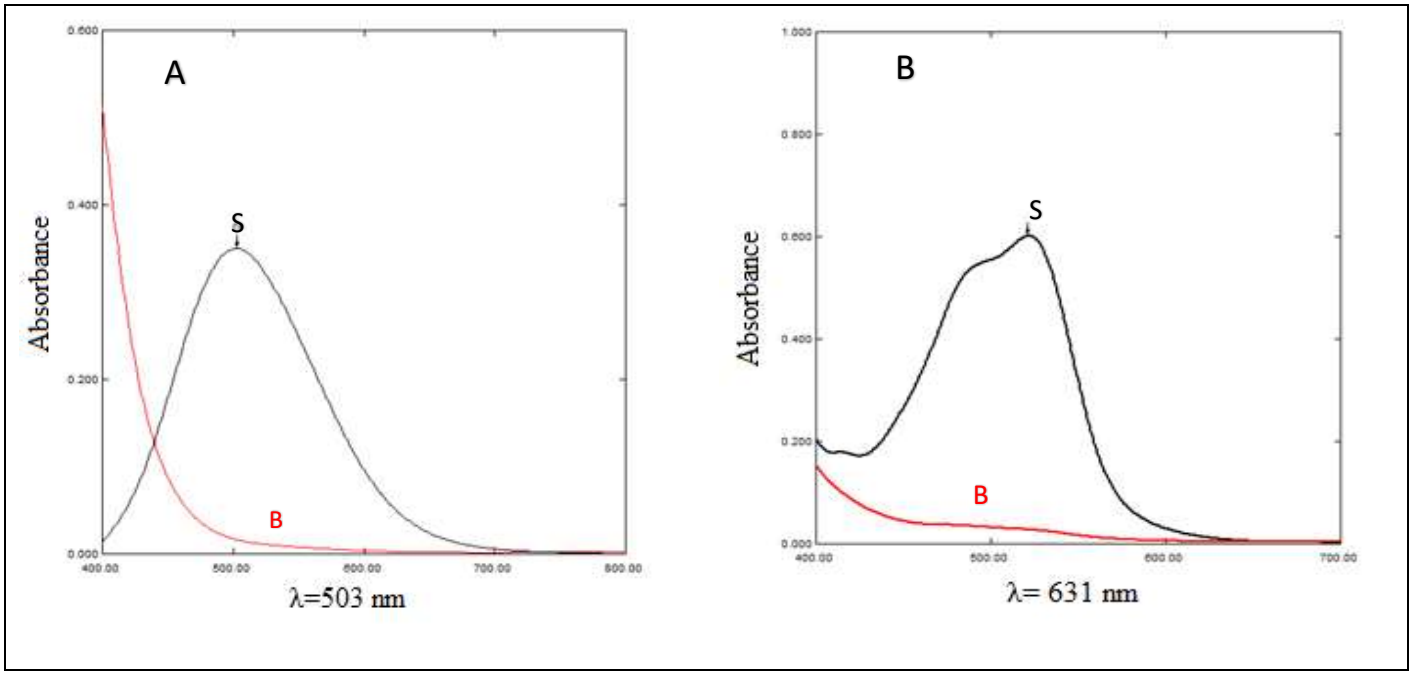
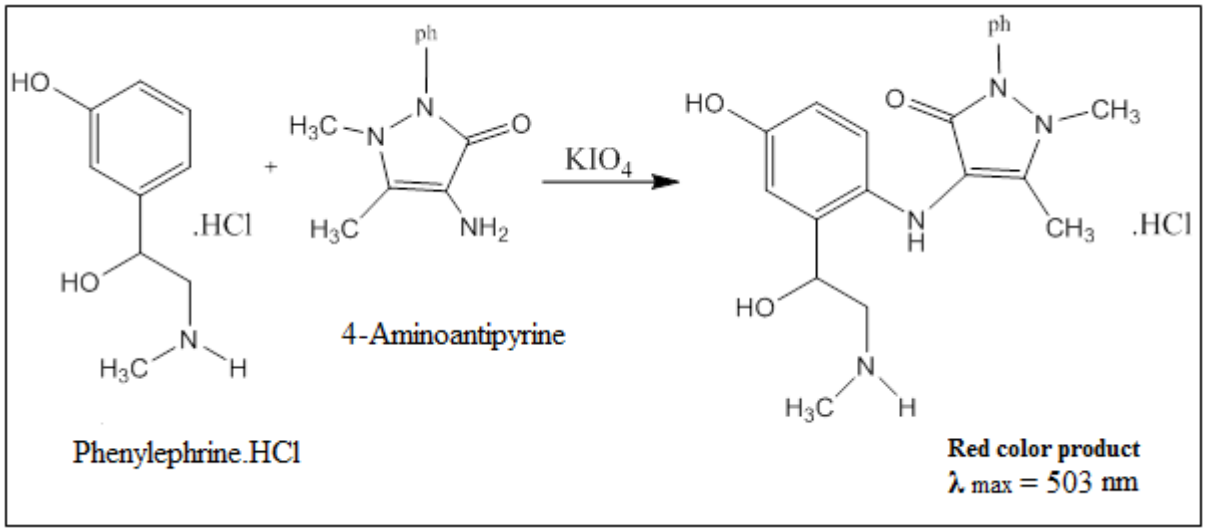
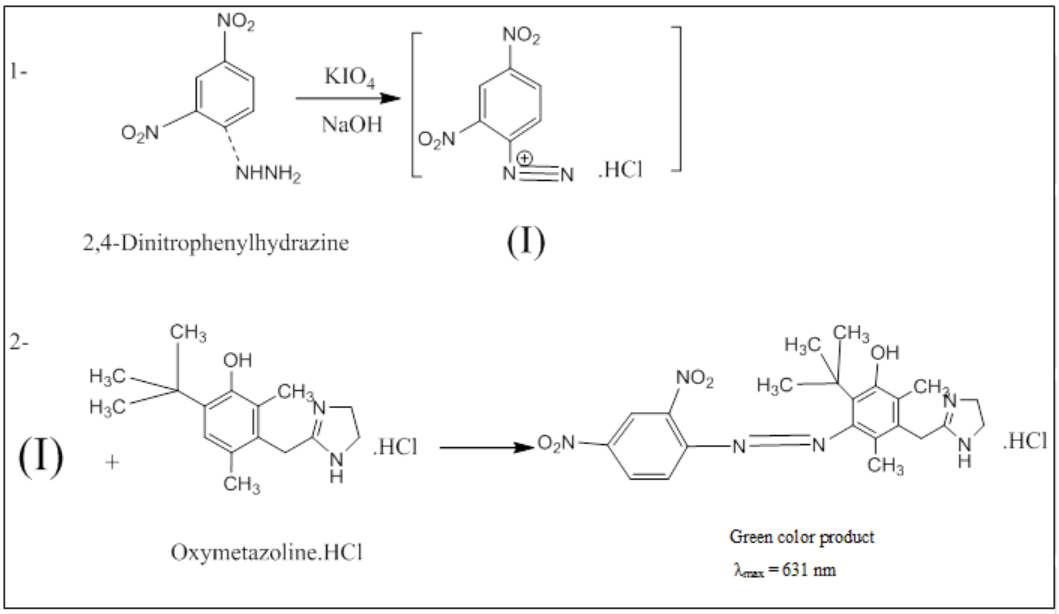


Figure 2. Absorption spectrum of A/ (PHE (10 µg. mL^{-1}) red colored complex against blank solution and blank against distilled water.

B/ (OXY (10 µg. mL^{-1}) green complex against blank solution and blank against distilled water.



Scheme 1. Suggest mechanism of the reaction between PHE.HCl with 4-AAP using classical method.



Scheme 2. Suggest mechanism of the reaction between OXY.HCl with DNPH using classical method**.**

2. Manifold of the proposed FI system

The chemical optimum conditions were studied for the decongestant drugs PHE and OXY. The first experiment was the best concentration of the reagent, as seen in Figures 3A-B and it was found that (3.9×10^{-2} M) for the PHE drug and (1×10^{-2} M) for the OXY drug. The second experiment is the best concentration of the oxidizing agent, as seen in Figures 4A-B, where it was found to be (4.8×10^{-3} M) for the PHE reaction and (2×10^{-3} M) for the OXY reaction. As for the third experiment, it was to study the best concentration of the basic medium for the OXY reaction, and it was found to be (0.8M), as seen in Figure 5, as shown in Figure 6A-B, the best addition sequence was studied, and it was found that the best sequence for the reaction of the PHE was (D in L1, R in L2, O in L3) and for the OXY reaction was (D in L1, R in L2, O&B in L3).

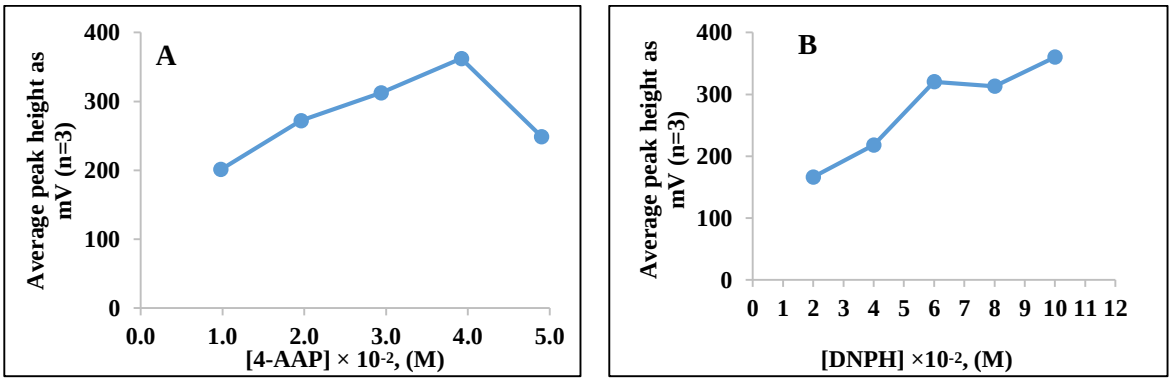


Figure 3. Chemical variables of the best concentration of reagent, A/PHE(4-AAP), B/ OXY(DNPH).

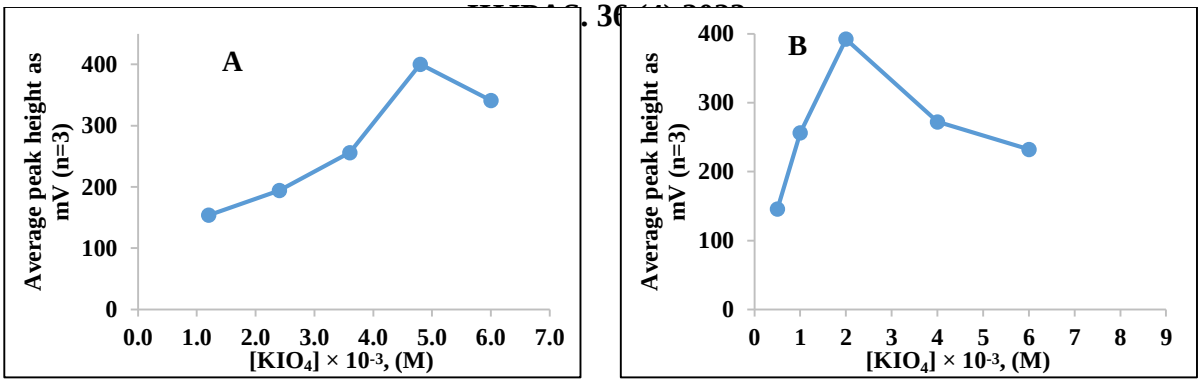


Figure 4. Effect of the best concentration of oxidizing agent (KIO_4), A/PHE, B/ OXY.

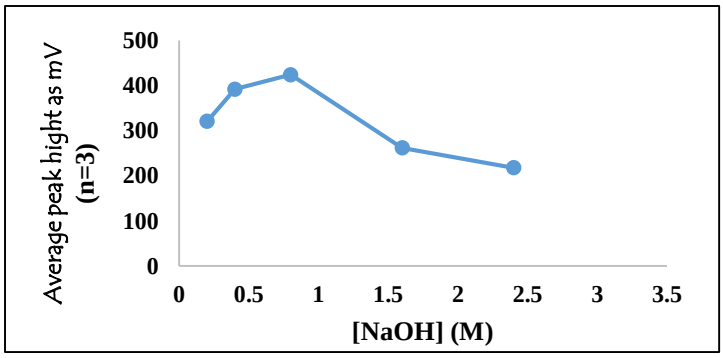


Figure 5. Effect of the best concentration of basic medium (NaOH).

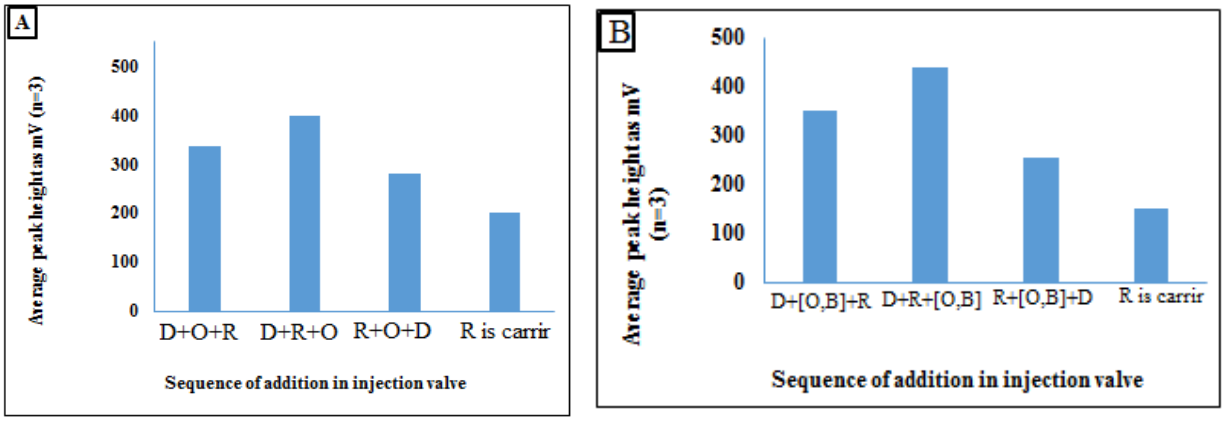


Figure 6. Study of the best sequence for the reaction of drugs, A/ (PHE), B/(OXY).

3.1 physical variables

As physical conditions, the loop volume, reaction coil length, and flow rate were studied, and it was found that the best loop size for the PHE reaction was (30-40-40 cm) equal (58.88-78.50-78.50 µL) and for OXY was (40-30-60 cm) equal (78.50-58.88-117.75 µL), as shown in Figures 7A-B. The best reaction coil length for the PHE and OXY reactions was 50 cm, as shown in Figures 8A-B. And the best flow rate for the PHE and OXY reactions was 3.1mL. min^{-1}, as shown in Figures 9A-B.

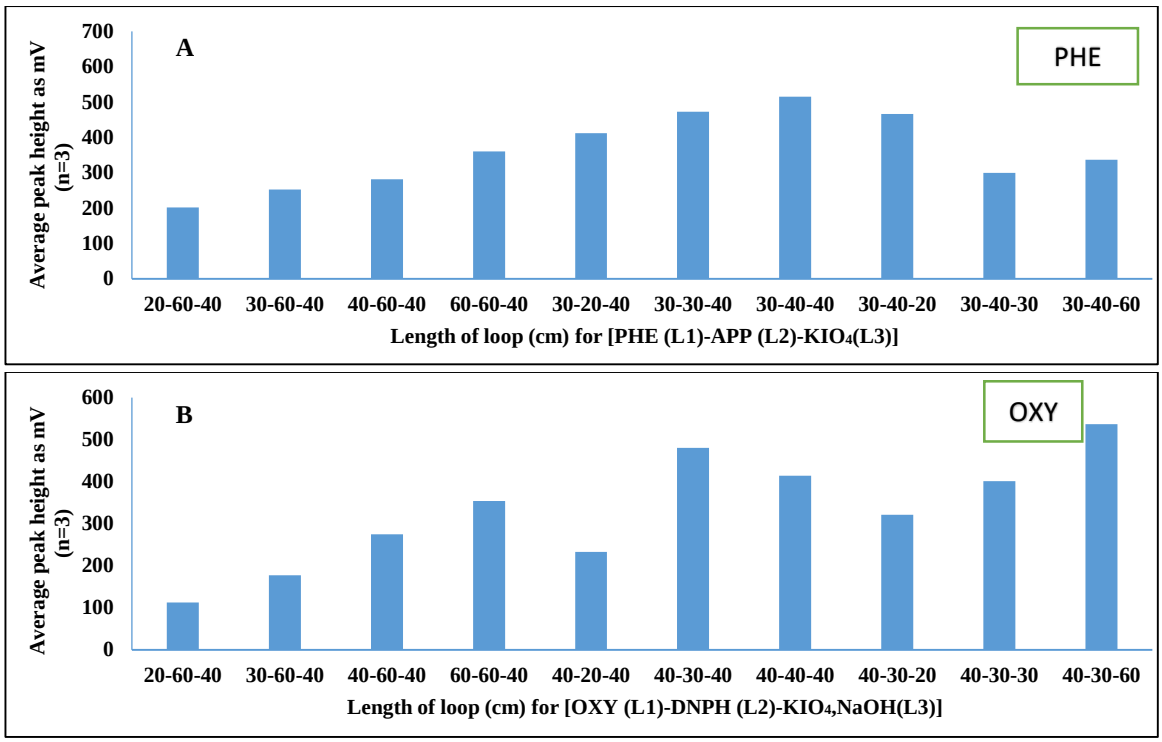


Figure 7-A-B. Effect of Injected volume.

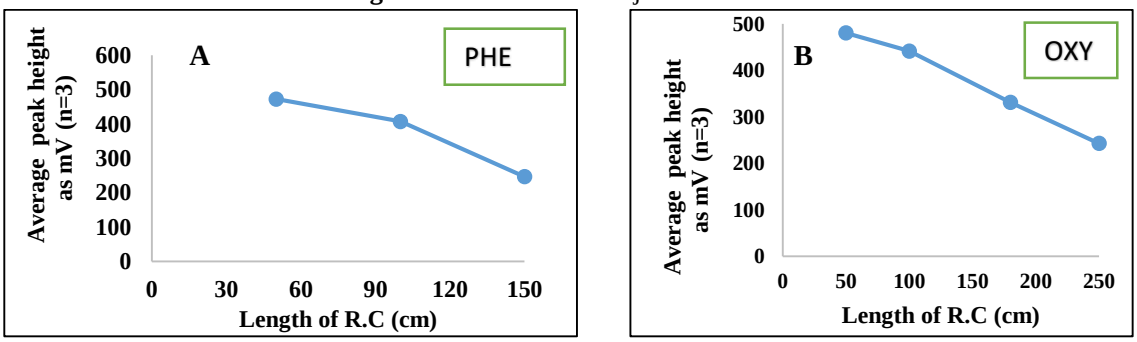


Figure 8-A-B. Effect of Reaction coil

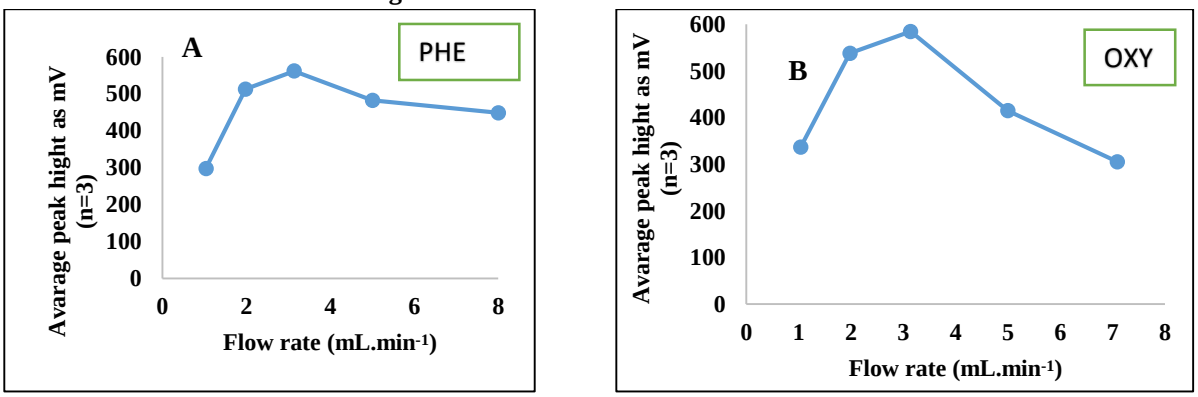


Figure 9-A-B. Effect of Total flow rate.

3.2 Dispersion of sample zone

In the FIA method, the sample interacts with several solutions and disperses throughout the solution, a phenomenon known as dispersion in physical terms [25]. Three concepts serve as the foundation for the FIA analytical technique's success: repeatable injection volume, repeatable injection duration, and control of sample zone dispersion, as shown in Tables 1 and 2. The dispersion of the reaction was 1.3 for PHE and 1.2 for OXY for different concentrations of the

drugs. The dispersion was evaluated using the equation D = C_o/C. When making contact outside of the flow injection system and reaching the top, the peak without dilution is Co, but the peak after dilution is C. The proper beaker was used to combine all the ingredients, and the resultant solution was then injected using the flow injection mechanism (as a carrier stream) (C_o). The second experiment consisted of injecting D, R, and O into L1, L2, and L3, respectively. The device uses distilled water as a carrier (mL.min^{-1}), and the injected component pushes the ingredients toward the detector before forcing them into the reaction coil, producing a response represented by (C).

Table 1. Dispersion value of PHE drug using the developed FI system

[PHE] µg.mL^{-1}	C_o (cm)	C (cm)	D
40	6.7	5.3	1.3
80	8.2	6.2	1.3

Table 2. Dispersion value of OXY drug using the developed FI system

[OXY] µg.mL^{-1}	C_o (cm)	C (cm)	D
60	7.4	6.2	1.2
100	9.0	7.5	1.2

3.3 Calibration curve

A series of concentrations in the range (1-800) µg.mL^{-1} of PHE and (1-600) µg.mL^{-1} of OXY were taken by diluting the stock solution (1000) µg.mL^{-1} and injecting it into the FI system. It showed that the range of concentrations is (10–600 of PHE, 5-400 of OXY) µg.mL^{-1}, as shown in Figures 10A–B, and (3,4) expressed as average peak height in mV (n = 3).

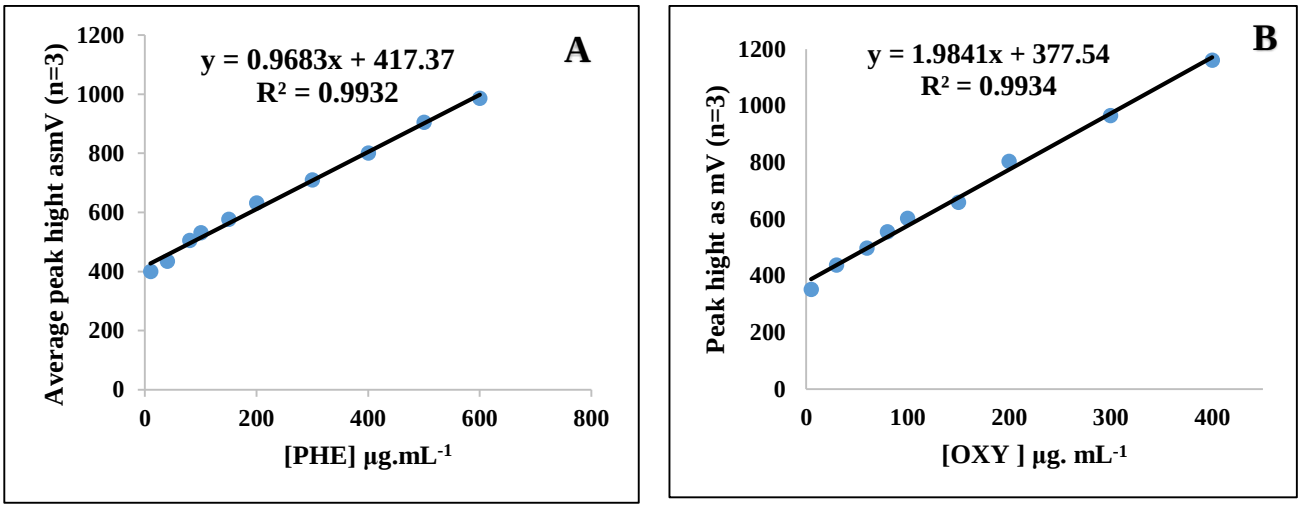


Figure 10-A-B. Linear dynamic range for determination of PHE, OXY using the developed CFIA system

Table 3. Linear calibration curve for determination of PHE drug using [PHE.HCl –4-AAP-KIO_4] FI system.

PHE (µg.mL^{-1})	Average response ($\bar{y}$) (mV)	RSD%	S.E.M	*E/y %
10	400	4.00	400±40	9.93
40	435	2.13	435 ±23	5.28
80	505	1.64	505 ±21	4.08
100	531	4.85	531 ±64	12.03
150	576	3.67	576 ±53	9.12
200	632	1.27	632 ±20	3.14
300	709	1.72	709 ±30	4.28
400	800	0.09	800±2	0.22
500	905	1.43	905±32	3.55
600	985	4.11	985±100	10.20

Table 4. Calibration curve for determination of OXY drug using [OXY.HCl –DNPH-KIO_4] FI system**.**

OXY (µg.mL^{-1})	Average response ($\bar{y}$) (mV)	RSD%	S.E.M	*E/y %
5	351	4.61	351±40.13	11.44
30	437	4.22	437±45.87	10.49
60	497	0.37	497±4.59	0.92
80	555	0.83	555±11.47	2.07
100	602	0.46	602±6.88	1.14
150	659	0.70	659±11.40	1.73
200	803	0.58	803±11.47	1.43
300	964	0.67	964±16.04	1.66
400	1160	0.02	1160±0.4702	0.04

$$\frac{E}{y}\% = t_{tab}\frac{SD}{\sqrt{n}} \times \frac{100\%}{\bar{y}}$$

3.4 Analysis of variance (ANOVA) and Repeatability

To compute $(yi - \hat{y}i)^2$ for (n-2) degrees of freedom, calculate the assumed error, called-for regression, and the sum of squares of the difference between the response's (yi) and the appraiser's $\hat{y}i$ values $(S_2)^2$.

Calculate the sum of squares of the variance of values $\hat{y}i$ from the average value (due to regression), [26,27] and then divide that result by the square root of the degree of freedom (1) to obtain the value (F), as shown in Tables 5 and 6.

Table 5. ANOVA for the developed FI technique[PHE].

Source of Variation	Sum. of Squares (SS)	Df	Mean of Squares (MS)	$F(\frac{S_1^2}{S_2^2})$	F_{crit}
Between Groups (Error)	2098388.744	1	$2098388.744=(S_2)^2$	106.2253218	4.413873419
Within Groups (Regression)	355574.3278	18	$19754.12932=(S_1)^2$		
Total	2453963.072	19			

Table 6. ANOVA for the developed FI technique[OXY].

Source of Variation	Sum. of Squares (SS)	Df	Mean of Squares (MS)	$F(\frac{S_1^2}{S_2^2})$	F crit
Between Groups(Error)	2017901.547	1	2017901.547=$(S_2)^2$	58.50147646	4.493998478
Within Groups (Regression)	551890.7676	16	34493.17297=$(S_1)^2$		
Total	2569792.314	17			

The repeatability of the proposed system was acceptable as shown in Table (7,8).

Table 7,8. Repeatability of consecutive measurement of PHE, OXY(n=8) using the developed FIA system.

OXY ($\mu g.mL^{-1}$)	Found ($\bar{x}$)	Error	Rec%	Erel%	RSD%
60	59.20	-0.79	98.66	-1.33	2.014
100	102.70	2.70	102.7	2.701	3.013

PHE ($\mu g.mL^{-1}$)	Found ($\bar{x}$)	Error	Rec%	Erel%	RSD%
40	40.49	0.49	101.2	1.234	3.59
80	79.39	-0.608	99.24	-0.76	3.27

3.5 Methods validation

The analytical characteristics of the new technique (CFIA/MZ) include limit of detection, correction factor, standard relative deviation(r), linear range [28,29], obtained under optimal conditions as shown in Table 9.

Table 9. Analytical characteristic of calibration curve for [PHE, OXY] drugs via FI system**.**

Parameters	PHE	OXY
λmax (nm)	503	631
Regression equation; y = bx+ a; y = absorbance; x = concentration (µg. mL^{-1})	y = 0.9683x + 417.37	y = 1.9841x +377.54
Linear range (µg mL^{-1})	10- 600	5-400
Average of recovery (%)	100.24	100.68
Average of Relative Error (Erel %)	0.24	0.68
Average of Relative standard deviation (RSD %)	3.44	2.51
Slope (b); (mL. μg^{-1}) $b = \Sigma i [(xi - \bar{x})(yi - \bar{y})]/\Sigma i(xi - \bar{x})^2$	0.97	1.98
Intercept (a); (a = y– b x)	417.37	377.54
Linearity (r^2%)	99.320	99.3400
Correlation coefficient (r): $r=\Sigma i [(xi - \bar{x}) (yi - \bar{y})] [(\Sigma i (xi - \bar{x})^2) (\Sigma i (yi - \bar{y})^2)]^{0.5}$	0.9966	0.9967
Standard deviation of slope (Sb) $Sb = Sy/x /[\Sigma i(xi - \bar{x})^2]^{0.5}$	0.028	0.061

Standard deviation of intercept (Sa) $Sa = Sy/x[\Sigma i\ xi^2 / (n\Sigma i(xi-\bar{x})^2)]^{0.5}$	8.665	11.773
Limit of detection (LOD)*	9.24	4.670
Limit of quantification (LOQ)**	30.809	15.567
Sample through put (h^{-1})	60	77
Standard deviation of the residuals; $Sy/x = [\Sigma i (yi - \hat{y}i)^2 / (n - 2)]^{0.5}$; $\hat{y}i = bxi+a$	17.2826	22.7516
Confidence limit of slope (b) = b ± tSb	0.9683 ± 0.0639	1.9841 ± 0.1413
Confidence limit of intercept (a) = a ± tSa	417.37 ± 19.5835	377.54 ± 27.1960

Table 10. Interferences effect on [PHE-AAP], [OXY-DNPH] via the developed FI system**.**

PHE					**OXY**			
Type of Interference	**conc. of Interferences ($\mu g.mL^{-1}$)**	**Average response ($\bar{y}$) (mV)**	***Erel %**	***Rec %**	**conc. of Interferences ($\mu g.mL^{-1}$)**	**Average response ($\bar{y}$) (mV)**	***Erel %**	***Rec %**
Sucrose	50	515	0.4819	100.48	40	542	3.378	103.38
	100	513	-0.7298	99.27	80	539	1.5498	101.55
	200	511	-3.775	96.22	160	536	-0.2360	99.76
Cellulose	50	518	3.6340	103.63	40	531	-3.4953	96.50
	100	513	-1.0162	98.98	80	533	-1.848	98.15
	200	515	0.4819	100.48	160	536	-0.116	99.88
Lactose	50	512	-2.272	97.73	40	539	1.595	101.60
	100	513	-0.8950	99.10	80	537	0.755	100.76
	200	514	-0.1102	99.89	160	542	3.695	103.70
Glucose	50	515	0.4819	100.48	40	535	-0.8409	99.16
	100	518	3.5113	103.51	80	536	-0.336	99.66
	200	513	-1.1704	98.83	160	531	-3.528	96.47
Sodium citrate	50	511	-3.676	96.32	40	530	-4.101	95.90
	100	511	-3.8032	96.20	80	532	-2.768	97.23
	200	511	-3.0817	96.92	160	534	-1.595	98.40

*Average three determinations

3.6 Effect of interferences

To evaluate the efficacy of the suggested method, interferences including glucose, sucrose, lactose, cellulose, and sodium citrate were tested. The pure sample of PHE is 100 $\mu g.mL^{-1}$ spiked with half, equal, and a double increment of the concentration of the interferences. As for OXY, the concentration of the pure sample is 80 $\mu g.mL^{-1}$ spiked with a half, equal, and double-fold excess concentration of selected interferences. Through the results shown in Table 10, the small error values, the absolute error, and the increase in the concentration of interfering do not affect the value of the response intensity with high recovery of the drugs. We did not notice that there is any interference when estimating the drugs PHE and OXY using the CFIA technique.

3.7 Applications and assessment of suggested method

The suggested method identified three PHE-containing dosage forms, as shown in Table 11. The statistical results were compared between the proposed method and the Official Method of Analysis of AOAC International [30, 31]. Using the F-test and student t-test, the calculated F-test

values were 0.1495 and 3.2751, and the t-test values were 0.6427 and 1.0106 less than the theoretical (critical) F-test (19.00) and t-test (2.78) via CFIA/MZ, so there is no fundamental difference between the proposed method for estimating drugs and the standard method.

And two pharmaceuticals containing OXY were examined by the FI method, as shown in Table 12. The statistical results were compared between the proposed method and the official British pharmacopeia method [32]. The calculated F-test values were 1.7060 and 0.9137, and the calculated t-test values were 0.0124 and 0.0532 less than the theoretical (critical) F-test (161.4) and t-test (4.30). The FIA technique was applied using successful determination for 100 µg.mL^{-1} of PHE and OXY in human plasma samples at high sampling/h. Accuracy and precision were tested three times for each concentration, with high repeatability of the result obtained as shown in Table 13.

Table 11. Application of the suggested method were compared to the official method for estimating PHE in Dosage forms.

Dosage form	Proposed FIA method conc. of PHE (µg.mL^{-1})					Official method (theoretical) conc. of PHE (µg.mL^{-1})				
	Present	Found	Erel%	Rec%	RSD%	Present	Found	Erel%	Rec%	RSD%
Rinoraz 5 mg,	20	20.15	0.75	100.75	1.24	20	19.47	-2.65	97.35	3.31
	30	29.84	-0.53	99.47	1.27	30	30.17	0.57	100.57	0.70
Nazafrine 10mg,	20	19.68	-1.60	98.40	1.27	20	20.14	0.70	100.70	3.20
	30	30.43	1.43	101.43	1.25	30	29.78	-0.73	99.27	0.71
Nazophen 10 mg,	20	19.77	-1.15	98.85	1.26	20	20.76	3.80	103.80	3.11
	30	30.55	1.83	101.83	1.24	30	30.11	0.37	100.37	0.70
$t_{tab} = 2.78\ for\ n_1 = n_2 = 3, n_1 + n_2 - 2 = 4, at\ 95\%\ confidence\ level$ $F_{tab} = 19.00\ for\ n_1 - 1 = n_2 - 1 = 2, at\ 95\%\ confidence\ level$										

Table 12. Application of the suggested techniques were compared to the official method for estimating OXY in Dosage forms.

	conc. of OXY µg.mL^{-1}					conc. of OXY µg.mL^{-1}				
	Present	Found	Erel%	Rec%	RSD%	Present	Found	Erel %	Rec%	RSD%
Oxymetazoline-MUP 0.5 mg	10	10.39	3.90	103.90	4.36	10	9.82	-1.80	98.20	3.53
	20	19.78	-1.10	98.90	2.32	20	20.47	2.35	102.35	2.35
Alerjon 0.25 mg	10	9.75	-2.50	97.50	4.64	10	10.31	3.10	103.10	3.36
	20	20.43	2.15	102.15	2.25	20	19.79	-1.05	98.95	2.43
$t_{tab} = 4.30\ for\ n_1 = n_2 = 2, n_1 + n_2 - 2 = 2, at\ 95\%\ confidence\ level$ $F_{tab} = 161.4\ for\ n_1 - 1 = n_2 - 1 = 1, at\ 95\%\ confidence\ level$										

Table 13. Determination of PHE and OXY in plasma samples using suggest FI system**.**

Sample of (PHE)	Added (µ) µg.mL^{-1}	Found ($\bar{x}$) µg.mL^{-1}	Erel%	Rec%	RSD%
1	100	99.79	-0.2065	99.79	1.69
2	100	103.20	3.2015	103.20	1.88
3	100	103.51	3.5113	103.51	2.07
4	100	101.87	1.8740	101.87	2.27
5	100	99.79	-0.2065	99.79	2.47
6	100	103.04	3.0414	103.04	2.65
7	100	104.96	4.9571	104.96	2.83

Sample of (OXY)	Added (µ) µg.mL^{-1}	Found ($\bar{x}$) µg.mL^{-1}	Erel%	Rec%	RSD%
1	100	98.77	-1.2348	98.77	1.52
2	100	97.79	-2.2106	97.79	1.70
3	100	101.59	1.5876	101.59	1.85
4	100	104.56	4.5613	104.56	2.00
5	100	97.25	-2.7468	97.25	2.23
6	100	99.02	-0.9833	99.02	2.39
7	100	99.52	-0.4789	99.52	2.56

3. Conclusion

According to the flow injection analysis literature, few studies have employed this novel approach to identify decongestant drugs (PHE, OXY) in pharmaceutical preparations and biological samples. The idea of this research is to suggest a developed, easy, fast, repeatability of the analytical data and an economical method for the determination of these drugs. The manifold FI system consists of a modified sensor designed for a homemade spectroscopic estimation as well as a locally manufactured value to accommodate 6-7 materials with the least consumption of chemicals and toxic reagents, with a stream carrier for materials using distilled water.

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